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09 May 2003

Pia Højbye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

NOVEL METHOXYBENZAMIDE COMPOUNDS FOR USE IN MCH RECEPTOR RELATED DISORDERS III

Field of the Invention

The present invention relates to novel compounds that interact with a melanin-concentrating hormone receptor, a MCH receptor. The compounds have modulating activity on the MCH receptor such as e.g. antagonistic, agonistic or allosteric activity and are useful for medicinal or cosmetic purposes such as, e.g. in the treatment or prevention of feeding disorders like obesity, metabolic syndrome, Type II diabetes, bulimina etc. or in the treatment or prevention of depression.

The invention also relates to therapeutic and/or prophylactic use of the compounds, to processes for the preparation of the novel compounds, to pharmaceutical compositions comprising the compounds, to the manufacture of such compositions and to methods for the treatment and/or prevention of MCH receptor related disorders.

Background of the Invention

Melanin-concentrating hormone (MCH) is a cyclic peptide that originally was isolated from salmoid pituitaries. In the fish, the 17 amino acid peptide causes aggregation of melanin and inhibits the release of ACTH. Mammalian MCH (19 amino acids) is highly conserved between rat, mouse and human exhibiting 100% amino acid identity. In the last decades there has been increasing activity in the research in the physiologic roles of MCH. It has been reported that MCH is involved in the feeding or body weight regulation, in energy balance, in response to stress, in water balance, in energy metabolism, in the general arousal/attention state, memory and cognitive functions and in psychiatric disorders. The biological effects of MCH are believed to be mediated by specific MCH receptors, and the MCH1 and MCH2 receptors have been described. Antagonists of MCH receptor (e.g. MCH1 receptor) may be suitable for use as obesity or weight reducing agents and they are also believed to have antidepressant and/or anxiolytic properties.

The present invention provides novel compounds that have a MCH modulating activity, i.e. antagonistic, inverse agonistic/negative antagonism, allosteric modulator, partial agonist or agonistic action.

Detailed description of the invention

The term "alkenyl" is intended to indicate an unsaturated alkyl group having one or more double bonds.

The term "alkynyl" is intended to indicate an unsaturated alkyl group having one or more triple bonds.

The term "cycloalkyl" is intended to denote a cyclic, saturated alkyl group of 3-7 carbon atoms.

The term "cycloalkenyl" is intended to denote a cyclic, unsaturated alkyl group of 5-7 carbon atoms having one or more double bonds.

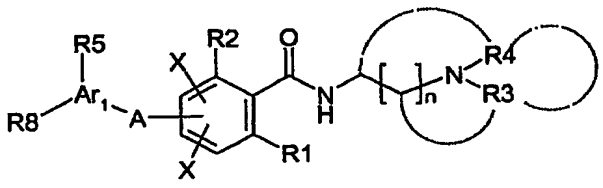
The term "alkoxy" is intended to indicate the group alkyl-O-.

The term "aryl" is intended to denote an aromatic (unsaturated), typically 6-membered, ring, which may be a single ring (e.g. phenyl) or fused with other 5- or 6-membered rings (e.g. naphthyl or indole).

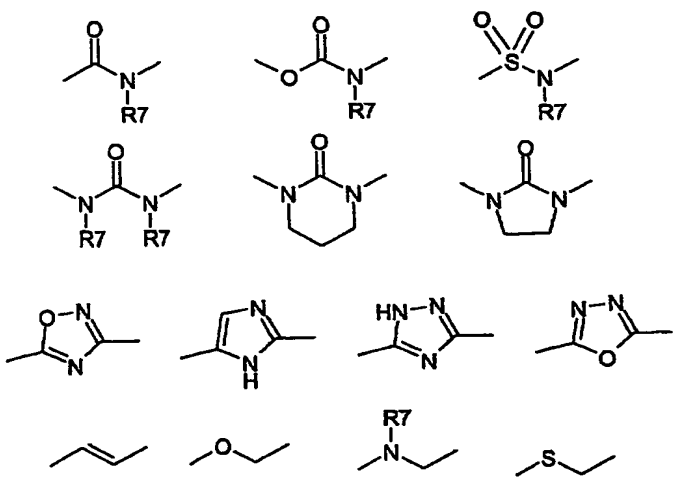
The term "heteroaryl" is intended to denote an aromatic (unsaturated), 5- or 6-membered, ring, which may be a single ring (e.g. pyridyl) or fused with other 5- or 6-membered rings (e.g. quinoline or indole).

The term "heterocyclyl" is intended to indicate a cyclic unsaturated (heteroalkenyl), aromatic ("heteroaryl") or saturated ("heterocycloalkyl") group comprising at least one heteroatom.

The present invention relates to a compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of



and, wherein the linker may be attached via either of the two free bonds to the Ar1 group;

and R7 is the same or different and is hydrogen or a straight or branched C_1-C_4 alkyl or alkenyl group;

Ar_1 is a aryl or heteroaryl group such as, e.g. phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R1 is a lower alkoxy group alkyl-O- with one to four carbon atoms and preferably one carbon;

R2 is an R1 group or a hydrogen, OH or NH_2 group;

R3 and R4 are the same or different selected from straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms; cycloalkyl groups with 3-7 carbons; alkylcycloalkyl with 4-9 carbons atoms; alkylaryl groups such as benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups such as 2-ethylpiperazine, 3-propylpiperidine; alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents such as Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, -$CONH_2$, -CONHAlk, -$CONAlk_2$, aryl, substituted aryl, benzyl, substituted benzyl groups;

Alk is the same or a different alkyl, alkenyl or alkynyl group;

R3 or R4 may optionally be linked to each other, when possible, as indicated in Formula I; and oxygen or nitrogen atoms may be inserted in the chain or ring in a chemically stable position;

R5 may the same or different selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3, -SO_2NH_2, -SO_2NHAlk, -SO_2NAlk_2, -SO_2Alk;

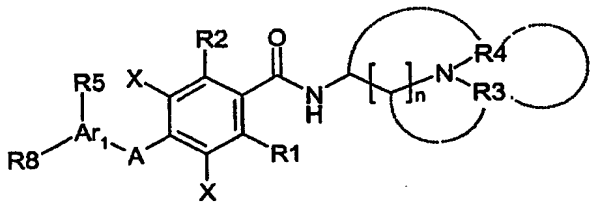
R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, -CF_3, -OCF_3, -SCF_3, -SCH_3;

more than one R5 group, same or different, or more than one R8 group, same or different, may be present on Ar1; when more than one R5 and R8 group are present they could be connected to each other to form rings. For example, a vinyl group could be joined with an amine group on a phenyl to form an indole system; a methoxy group could be joined with a phenol group to form a metylendioxyaryl system;

X being the same or different H, F, Cl, Br, I, CF_3, OCF_3, SCF_3, SCH_3, OCH_3 or lower alkyl or alkenyl group;

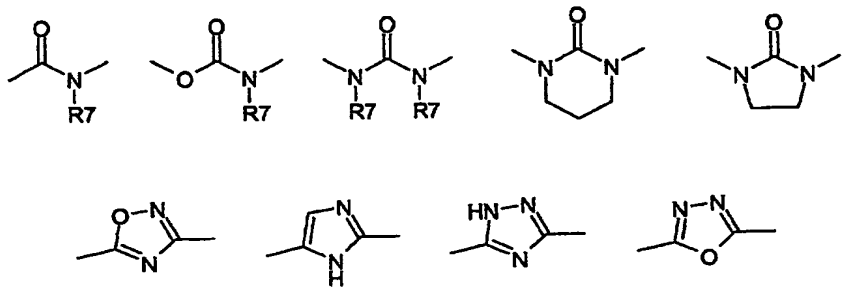
n is 1,2 or 3.

In another embodiment, the invention relates to a with the following structure (Formula Ia)

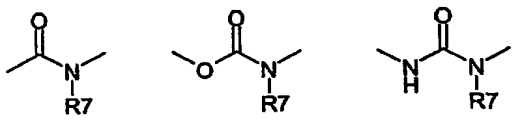


wherein Ar_1, A, B, R1, R2, R3, R4, R5, R8, n and X are as defined above.

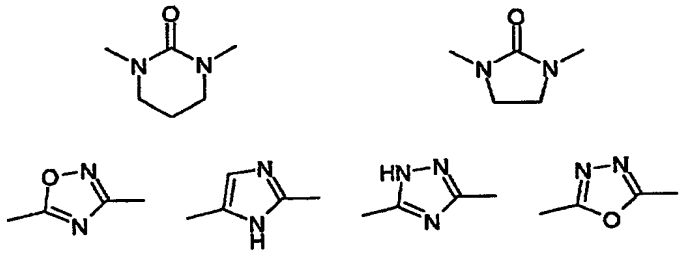
-A- may be selected from the group consisting of



or from the group consisting of



Furthermore, the –A- moiety may be selected from the group consisting of



In specific embodiments, R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -$CONAlk_2$, -NHCO-Alk, -CO-Alk, -CF_3, -OCF_3, -SCF_3, -SCH_3. Alternatively, R8 is aryl groups (Ar), heterocyclyl groups, heteroaryl groups, alkylaryl groups, alkylheteroaryl groups, alkylheterocyclyl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), -CONHAr, -NHCO-Ar, or -CO-Ar.

Ar_1 may be an aryl, heterocyclyl or heteroaryl group such as, e.g. phenyl, pyridine, thiophene, R2 hydrogen and/or R2 is hydrogen and X is F, Cl, Br, I, CF_3, OCF_3, OCH_3, SCF_3, SCH_3 or Alk.

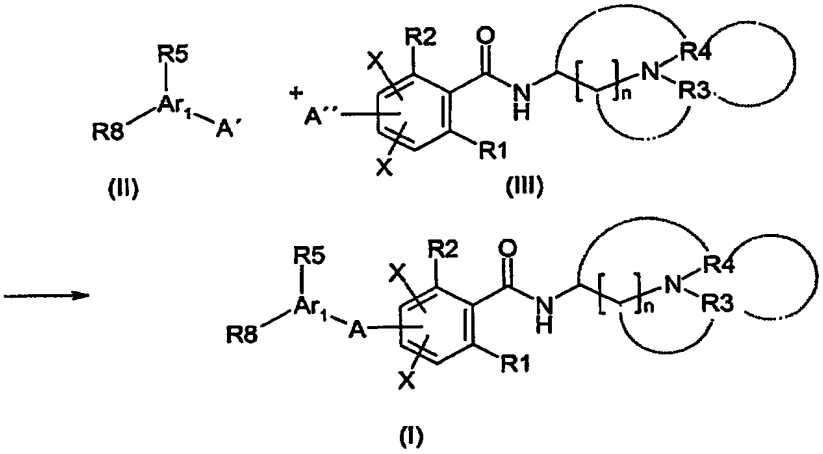
Alternatively, R2 is OH and X is F, Cl, Br, I, CF_3, OCF_3, SCF_3, SCH_3 or Alk.

R5 may be selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), nitrile, lower alkyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3.

Other specific embodiments appear from the appended claims and the examples herein.

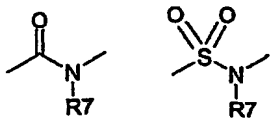
Synthetic routes

Compounds of formula I are preferably made by connecting an appropriately functionalised (A'') benzamide moiety III with a suitably functionalised (A') aryl moiety II using well-known synthetic routes according to the following general scheme (Route 1):



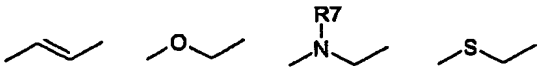
For example, urea bonds -A- can be formed by reaction of II having A' as isocyanate with III having A'' equal to NH-R7 using appropriate catalysis by base or acid. The reverse use of III having A'' as isocyanate with II having A' equal to NH-R7 can also be applied. Analogously, carbamates can for example be made by reaction of II having A' as isocyanate with III having A'' equal to OH or the reverse use of OH and isocyanate in A' and A''.

Preparation of amide and sulphonamide bonds



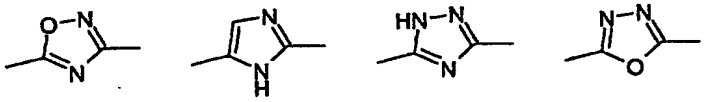
in the connecting A-linkage can be made via reaction of A'' in compound III being NH-R7 with activated forms, e.g. acid chlorides or active esters, of A' in compound II being COOH or SO_2OH. Alternatively, the conversion can be made directly with the acids having A' as COOH using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), and promoters such as 1-hydroxybenzotriazole. The reverse use of A' and A'' in II and III can be applied as well to form the linker in the opposite direction.

Formation of the connecting A-linkage to form

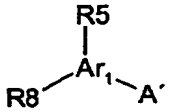


bonds in either direction between Ar1 and the benzamide can be made by N-, O- or S-alkylations of compound II with A' being OH, NH-R7, or SH with compound III with A'' being a CH_2-L wherein L being a suitable leaving group such as halogen (Cl, Br, I), tosyl or mesyl using appropriate catalysts and conditions. The alkene linkage can be made by a Wittig reaction with compound II with A' being CHO and compound III with A'' being CH_2-PPh_3. The reverse use of A' and A'' in II and III can be applied as well to form the linker in the opposite direction.

The 5-membered heterocyclic linkers



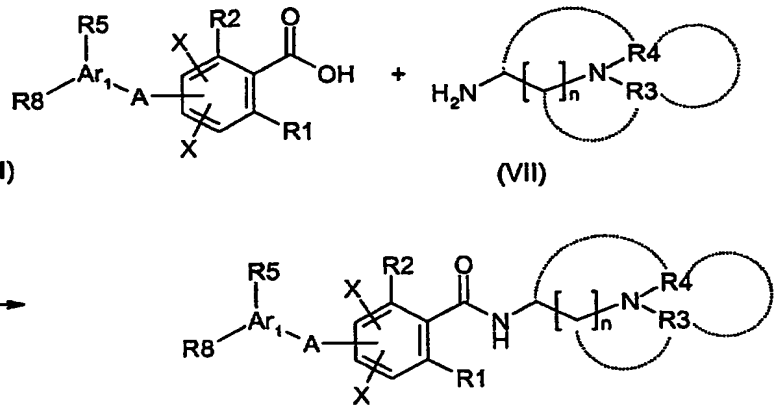
can be made according to standard cyclisation procedures using appropriate solvents, catalysts and temperatures. For example, formation of 1,2,4-triazole can be made from II with A' being acylhydrazide with III with A'' being amide or thioamide or the reverse orientation of A' and A''. 1,2,4-Oxadiazole can be formed from II with A' being amidoxime with III with A'' being carboxylic ester or the reverse orientation of A' and A''. 1,3,4-Oxadiazole can be formed from II with A' being acylhydrazide with III with A'' being carboxylic ester or the reverse orientation of A' and A''.



(II)

Aromatic substituents R4, R5 and R8 are preferably introduced prior to formation of the A- or B-linkage either direct or via a masked functionality that is compatible with the subsequent synthetic steps.

Compounds of formula I are also obtained by connecting carboxylic acid derivatives VI with amines VII using well-known synthetic routes according to the following general scheme (Route 2):

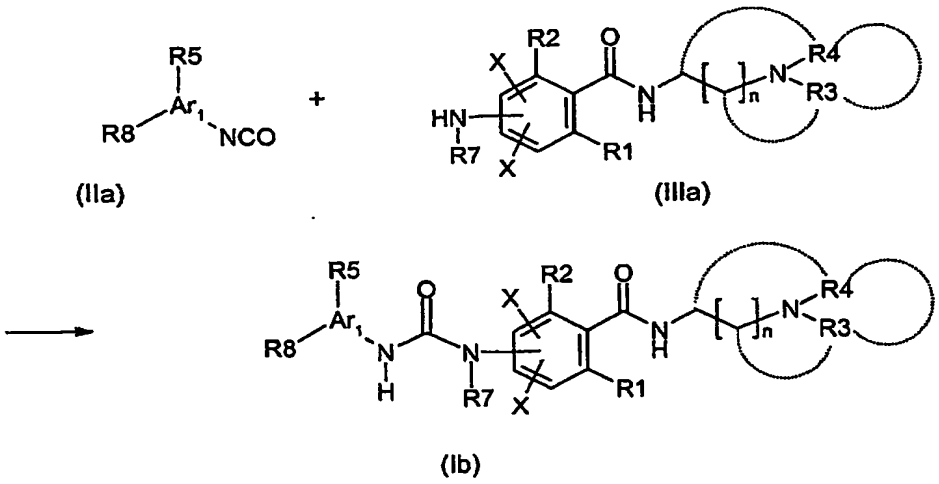


Thus, the benzamide bond is formed by reacting a suitably activated carboxylic acid VI (e.g. acid chloride) with the corresponding amines VII in the presence of a base or using suitable coupling reagents such as DCC in presence of promoting agents and a suitable base.

Alternatively, compounds of formula I can be made by N-alkylation of compounds of formula I having R3 and R4 being hydrogen using well-known synthetic routes such as reductive alkylation or alkylation with alkyl halides in case the functionalisation of the molecule is compatible with this type of reactions (Route 3).

Synthetic method 1A

Thus, compound (Ib) having NHCON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced, for instance, by the following urea reaction.



(IIa) (IIIa)

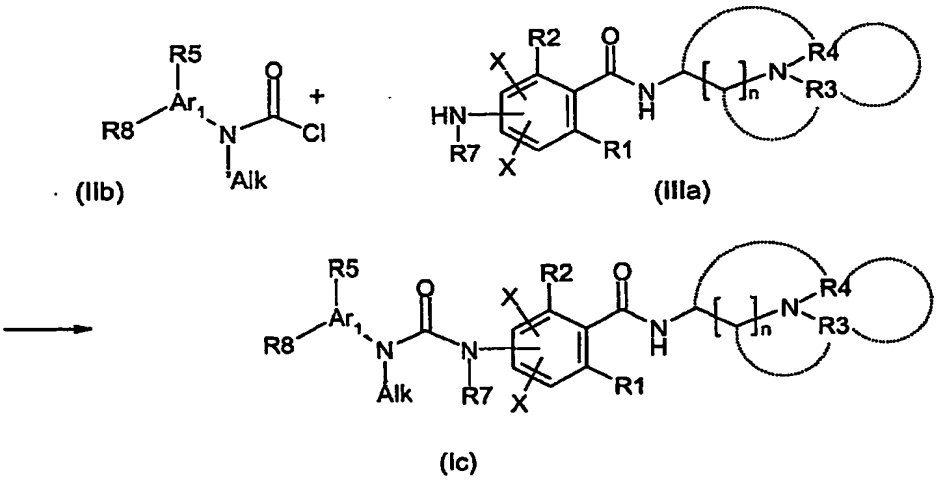
(Ib)

Compound IIa and compound IIIa are reacted in an inert solvent in accordance with standard procedures. Typically, inert solvents can be ether solvents, halogenated hydrocarbon solvents, nitrile solvents and aromatic solvents. Reaction temperature is usually room temperature and the reaction time is 2 hours to 1 day.

Compound IIa can be produced from the corresponding carboxylic acid. For instance, 4-phenoxyphenylisocyanate can be produced in accordance with methods such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley); R.C. Larock.

Synthetic method 1B

Compound Ic having N-AlkCON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced, for instance, by the following urea reaction.



(IIb) (IIIa)

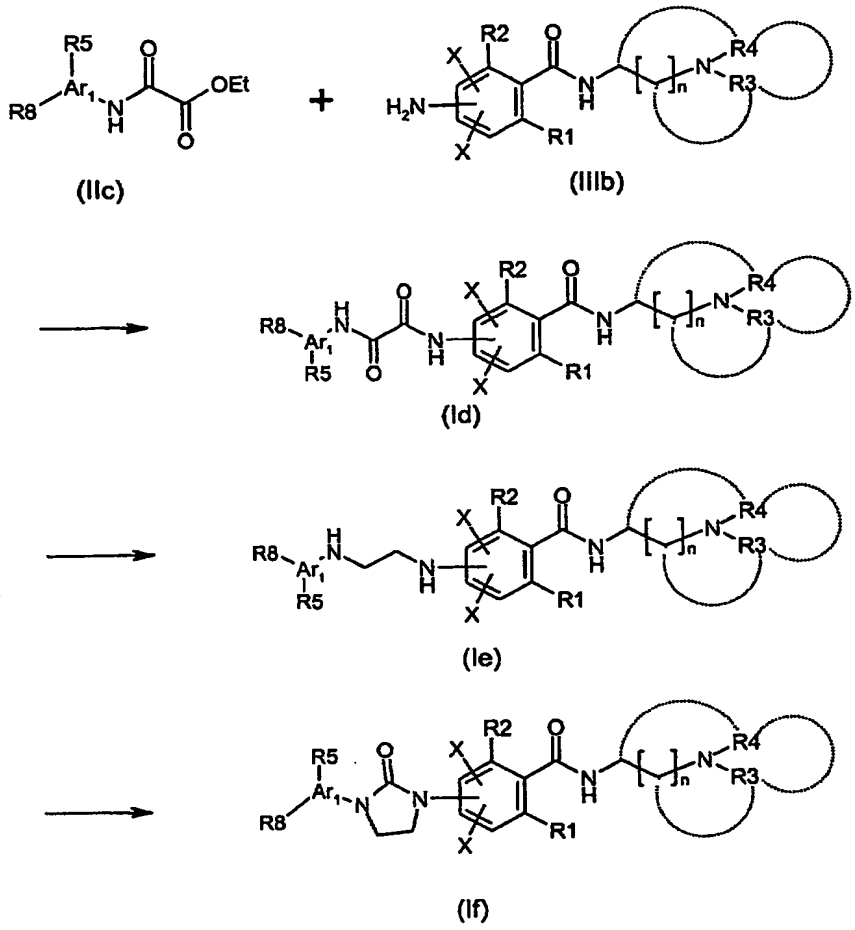
(Ic)

Compound IIIa and 1 equivalent of compound IIb are reacted in an inert solvent in the presence of an excess of a base in accordance with known procedures (e.g. WO 9205174; *J.Med.Chem.* 43(20), 3653-3664, 2000). Suitable inert solvents can be ether solvents, halogenated hydrocarbon solvents, nitrile solvents and aromatic solvents. As a base can be used for instance triethylamine, diisopropylethylamine and sodium carbonate. Typically, the reaction temperature is 0 °C to room temperature and the reaction time is 1 hour to 1 day.

Compound IIb can be produced from the corresponding N-alkyl aromatic amine by well-known methods. For instance, N-methyl-N-4-phenoxyphenylcarbamoyl chloride can be produced in accordance with methods such as described in *J. Labelled Compd. Radiopharma* 29(2), 149-155, 1991.

Synthetic method 1C

Compound If having 5-membered ring urea as linker A can be produced, for instance, by the following reaction sequence.

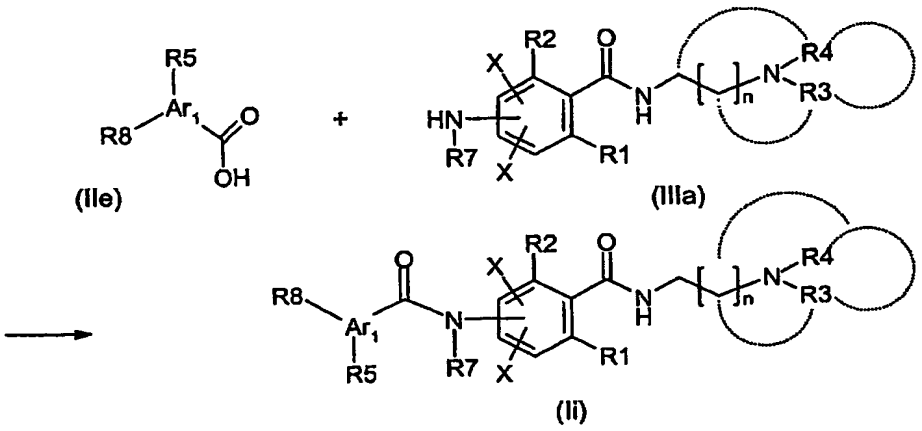


Compound Ie and 1 equivalent of carbonyldiimidazole are reacted in an inert solvent at elevated temperature until the reaction is completed. Typically, the reaction is conducted at reflux in acetonitrile for less than 24 hours.

Compounds IIc, Id and Ie can be produced following the functional group conversions described in procedures like the one in *J.Med.Chem.* 43(20), 3653-3664, 2000.

Synthetic method 1D

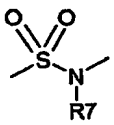
Compound Ii having CON-R7 as linker A with R7 defined as hydrogen or lower alkyl or alkenyl group, can be produced by the following amidation reaction.



The amide bonds are formed by reacting a suitably activated carboxylic acid IIe (acid chloride, mixed anhydrides, esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine) with anilines IIIa in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, 4-dimethylaminopyridine (DMAP) and sodium carbonate. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

The coupling can also be performed directly from IIe using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-cabodiimide (EDCI), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) preferably in presence of promoting agents capable of forming an active ester such as 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, N-ethyldiisopropylamine, and 4-methylmorpholine. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

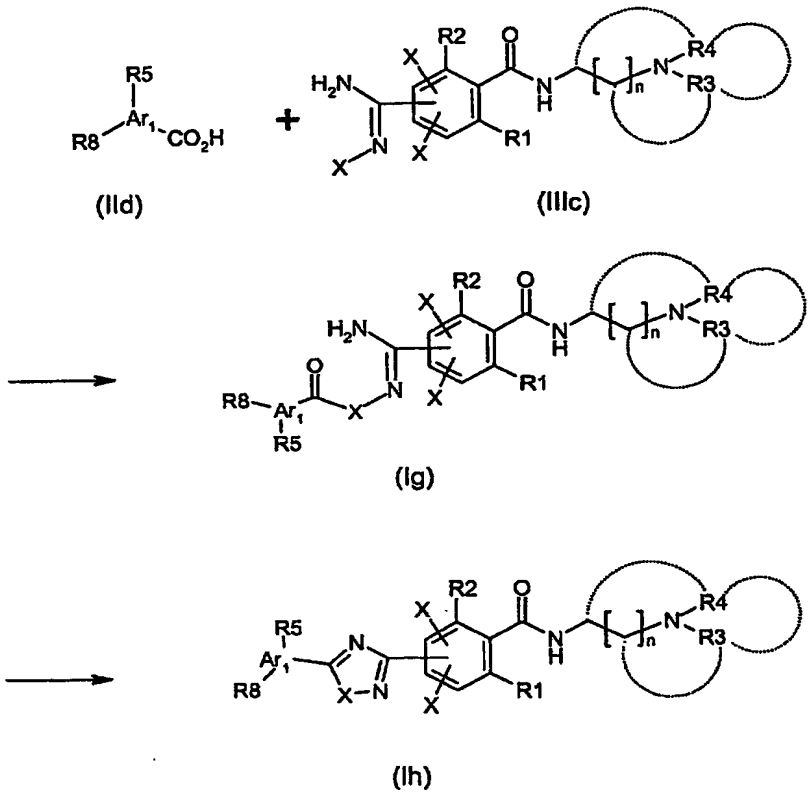
Analogously, a sulphonamide group, as the connecting A-linkage to form



bonds can be made via the corresponding reaction of Ar-NH-R7 (IIIa) with activated forms of sulphonic acids, such sulphonyl chlorides, in the presence of base.

Synthetic method 2

Compound Ih having 1,2,4-oxadiazole (X=O) or 1,2,4-triazole (X=NH) heterocyclic rings as linker A can be produced, for instance, by the following cyclodehydratation reaction.



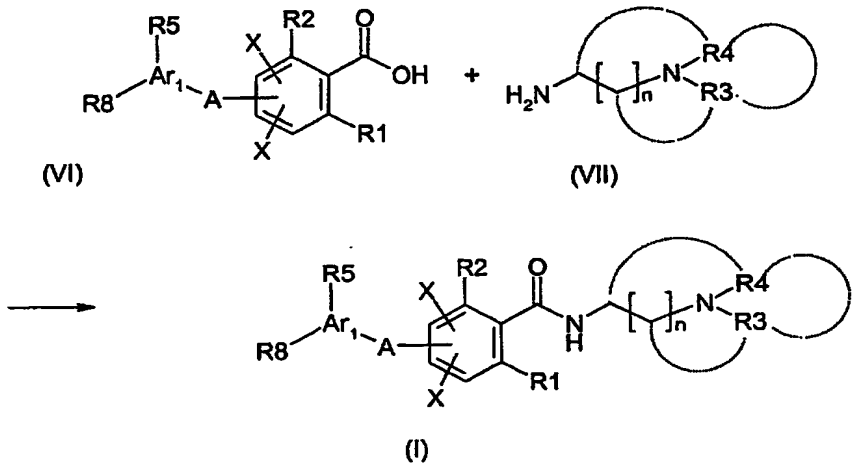
Compound Ig is reacted in an inert solvent with or without the presence of a suitable base or acid (e.g. N-tetrabutyl ammonium fluoride, sodium hydride, sodium ethoxide or polyphosphoric acid) in accordance with standard methods such as described in *Tetrahedron Lett.* 42, 1441-1443, 2001; *Tetrahedron Lett.* 42, 1495-1498, 2001. Suitable, inert solvents can be ether solvents, amide solvents and aromatic solvents. The reaction temperature is usually room temperature to 100°C and the reaction time is 1 hour to 3 days.

Compound Ig can be produced by reacting an activated derivative of compound IId with 1 equivalent of compound IIIc in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine and sodium carbonate.

Appropriate examples of the activated derivatives of compound IId include active esters (e.g. esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinamide), acid chlorides, symmetrical or unsymmetrical anhydrides and orthoesters. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

Compound IIIc can be produced from the corresponding amino compound IIIb by well known methods such as described in "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock; In "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky).

Synthetic method 3



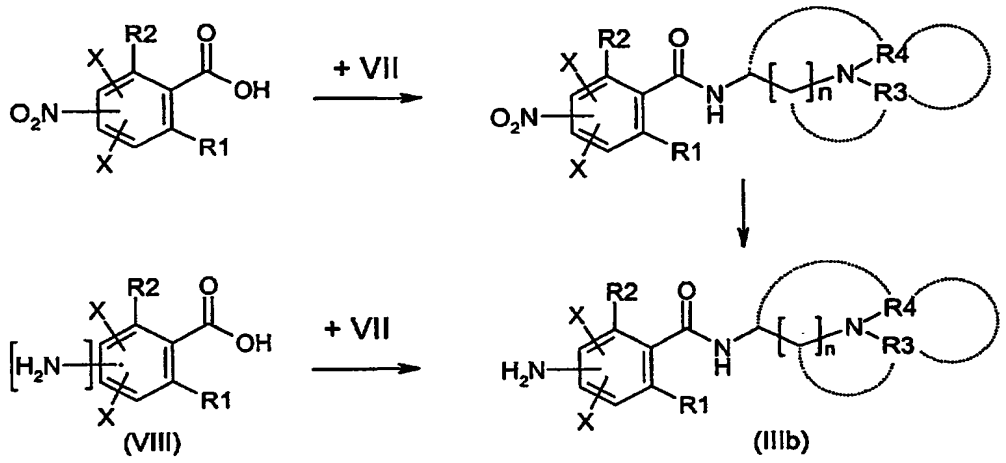
Benzamide bonds are formed by reacting a suitably activated carboxylic acid VI (acid chloride, mixed anhydrides, esters with phenol bearing electron withdrawing substituents, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 2-hydroxypyridine) with the corresponding amines VII in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, 4-dimethylamino-pyridine (DMAP) and sodium carbonate. . The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

The coupling can also be performed by using suitable coupling reagents such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-cabodiimide (EDCI), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) preferably in presence of promoting agents capable of forming an active ester such as 1-hydroxybenzotriazole, N-

hydroxysuccinimide, 2-hydroxypyridine in an inert solvent in the presence of a base. As inert solvents can be used ether solvents, amide solvents and halogenated hydrocarbon solvents. Suitable bases that can be used are triethylamine, diiisopropylethylamine, pyridine, N-ethyldiisopropylamine, and 4-methylmorpholine. The reaction temperature is usually between 0°C to 30°C and reaction time is 1 hour to 1 day.

Synthetic method 4

Intermediate IIIb



can be prepared by reacting an activated carboxylic acid derivative VIII according to methods described above, preferably having the aniline nitrogen suitably protected (e.g. Boc, CF_3CO), with the corresponding amine VII. The nitrogen may also be masked as a nitro group that subsequently is reduced to form IIIb. The N-alkylated derivative IIIa may be obtained via reductive alkylation of IIIb.

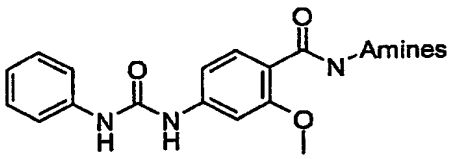
The carboxylic acids VIII are produced by well-known organic reactions including electrophilic substitutions or organometallic reactions such as ortho-lithiation and halogen-metal exchange followed by capture with electrophilic reagents. Alternatively, the aniline nitrogen may be introduced by a benzyne reaction.

Compounds

Below follows some examples of specific compounds according to the invention. In the compounds mentioned, one part of the molecule such as e.g. the amine group, the linker –A-, the Ar_1 group, the R4, R5, R8 group or the chain length is varied, while the other parts are conserved. Though not shown nor specifically mentioned, the invention also

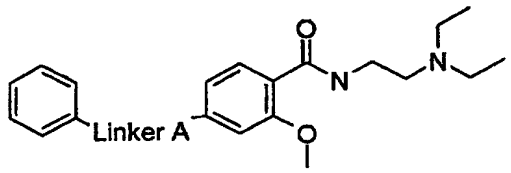
includes all compounds wherein all variations in one part of the molecule, e.g. linker –A- is combined with all variations in another of the features, e.g. variation in the Ar_1 group.

Variation of the amine



2-Methoxy-4-[3-phenyl-ureido]-*N*-(3-pyrrolidin-1-yl-propyl)-benzamide,
N-(4-Dimethylamino-butyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,
N-(3-Dimethylamino-2,2-dimethyl-propyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,
N-(3-Dipropylamino-propyl)-2-methoxy-4-[3-phenyl-ureido]-benzamide,

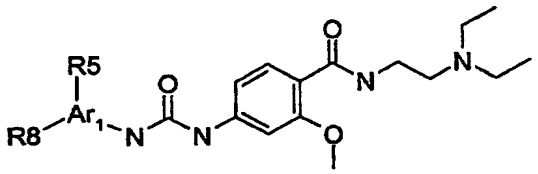
Variation of the linker A



N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzoylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzoyl)-amino]-benzamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy- N^4-(phenyl)-terephthalamide,
N^1-(2-Diethylamino-ethyl)-2-methoxy-N^4-methyl- N^4-(phenyl)-terephthalamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzenesulfonylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzenesulfonyl)-amino]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenylsulfamoyl)-benzamide,
N-(2-Diethylamino-ethyl)-4-[1,3-dimethyl-3-(phenyl)-ureido]-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(phenyl)-imidazolidin-1-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-methyl-3-(phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-oxo-3-(phenyl)-tetrahydro-pyrimidin-1-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(phenyl)-[1,2,4]oxadiazol-5-yl]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-4*H*-imidazol-2-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-1*H*-[1,2,4]triazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-[1,3,4]oxadiazol-2-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[5-(phenyl)-2*H*-[1,2,4]triazol-3-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(phenyl)-5*H*-imidazol-4-yl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[2-(phenyl)-vinyl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenoxymethyl)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzyloxy)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzylamino)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[methyl-(benzyl)-amino]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[(phenylamino)-methyl]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{[methyl-(phenyl)-amino]-methyl}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(phenylsulfanylmethyl)-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-(benzylsulfanyl)-benzamide

Variation of the aromatic rings as well as their substituents

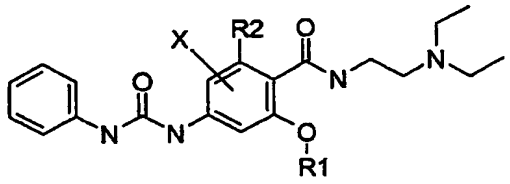


4-[3-(phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(5-indolyl)-ureido]-benzamide,
4-[3-(4-Benzofuranyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[3-pyridinyl]-ureido}-benzamide,
4-(3-[2,2']Bipyridinyl-6-yl-ureido)-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(pyridin-3-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-(8-quinolinyl)-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-phenoxy-pyrimidin-5-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(5-phenoxy-pyrazin-2-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-thiophenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-isothiazolyl]-ureido}-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-oxazolyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(1*H*-pyrazol-4-yloxy)-phenyl]-ureido}-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(5-bromo-thiophen-3-yl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-chloro-oxazol-4-yl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-trifuoromethyl-oxazol-2-yl)-ureido]-benzamide,
4-{3-[4-(4-Chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[3,4-Dichlorophenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-Fluoro-5-chlorothiophen-3-yl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-bromo-3-trifluoromethoxy-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[5-(3,4-methylenedioxy-phenoxy)-thiopen-3-yl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-(4-acetamido-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-trifluoromethyl-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-(4-methyl-phenyl)-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(4-hydroxy-phenoxy)-phenyl]-ureido}-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-4-{3-[4-(4-dimethylamino-phenoxy)-phenyl]-ureido}-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-(4-methylamino-phenoxy)-phenyl]-ureido}-benzamide,
4-{3-[4-(4-Cyano-3-chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-{3-[4-Carbamoyl-phenyl]-ureido}-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
4-[3-(3-Chloro-4-cyano-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(2-fluoro-3-methoxy-4-acetamido-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-bromo-6-methoxy-4-phenoxy-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-hydroxymethyl-4-trifluoromethyl-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-carboxamido-4-iodo-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-(*N*,*N*-dimethylcarboxamido)-4-chloro-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-trifluoromethoxy-phenyl)-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(3-trifluoromethyl-pyridin-2-yl)-ureido]-benzamide,

N-(2-Diethylamino-ethyl)-2-methoxy-4-{3-[4-trifluoromethoxy-thiophen-2-yl]-ureido}-benzamide,

Substituents on the benzamide moiety



N-(2-Diethylamino-ethyl)-2-ethoxy-4-[3-phenyl-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-benzamide,
3-Chloro-*N*-(2-diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-benzamide,
3-Bromo-*N*-(2-diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-benzamide,
2-Amino-3-chloro-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-phenyl-ureido]-benzamide,
2-Amino-3-bromo-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-phenyl-ureido]-benzamide,
2-Amino-*N*-(2-diethylamino-ethyl)-6-methoxy-4-[3-phenyl-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2,6-dimethoxy-4-[3-phenyl-ureido]-benzamide,
N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-3-trifluoromethyl-benzamide,
N-(2-Diethylamino-ethyl)-2-hydroxy-6-methoxy-4-[3-phenyl-ureido]-3-trifluoromethoxy-benzamide.

Salts, complexes or solvates

The invention also relates to physiologically acceptable salts, complexes, solvates or prodrugs of the compounds of the invention.

When a compound of the invention possesses a basic functional group it can form a salt with an inorganic or organic acid.

Examples of physiologically acceptable salts of the compounds according to the invention include salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

Examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid (to form e.g. a nitrate or a nitrite), sulfuric acid (to form

e.g., a H_2SO_3 salt, a sulfate or a H_2SO_5 salt) and phosphoric acid (to form e.g. a H_3PO_3 salt or a H_3PO_4 salt)

Examples of salts with organic acids include salts with formic acid, acetic acid, propionic acid, butyric acid, pentanoic acid, oxalic acid, tartaric acid, malonic acid, succinic acid, citric acid, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, acrylic acid, malic acid, fumaric acid, H_2CO_3, lactic acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and 3-chlorobenzoic acid.

Examples of salts with acidic amino acids include salts with aspartic acid and glutamic acid.

Optical isomers

When a compound of the invention contains optical isomers, diastereomers or other stereroisomers these are included as a compound of the invention as well as the racemate, i.e. mixture of enantiomers. Each of them can be obtained by methods known by a person skilled in the art. For example the optical isomer can be obtained using an optically active synthetic intermediate, an asymmetric synthesis or subjecting the racemic mixture of the final product or a suitable intermediate to optical resolution in accordance with known methods such as, e.g., fractional recrystallisation method, chiral column method, diastereomer method etc.

Other forms

The invention also encompasses a compound in amorphous, any polymorphous or any crystalline form.

Disorders

The compounds according to the invention can be used in medicine and modulate the activity of a MCH receptor. The compounds may be used as agents for preventing or treating diseases caused by or involving a melanin-concentrating hormone, i.e. they are useful for treating or preventing a MCH or MCH receptor related disorder or abnormality in a subject such as, e.g., an animal or a mammal such as, e.g., a human.

The compounds according to the invention may have antagonistic, inverse agonistic, agonistic or allosteric activity against a MCH receptor, normally antagonistic activity.

In the present context an agonist is defined as a compound that increases the functional activity of a MCH receptor (e.g. the signal transduction through a receptor). The term "agonist" includes partial agonist, i.e. which increases the functional activity of the receptor to a submaximal level. An inverse agonist (or negative antagonist) is defined as a compound that decreases the basal functional activity of a MCH receptor. An allosteric compound is defined as a compound that enhances or diminishes the effects of other receptor ligands.

An antagonist is defined as a compound that decreases the functional activity of a MCH receptor either by inhibiting the action of an agonist or by its own intrinsic activity.

The MCH receptors mentioned in the invention include MCH1 and MCH2 receptors. It also includes MCH receptors having at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequences CTLITAMDAN or CTIITSLDTC.

The MCH receptors may be an animal or a mammalian or non-mammalian receptor, such as a human receptor.

Increasing or decreasing the activity of a MCH receptor such as, e.g. a MCH1 receptor alleviates a MCH-related disorder or abnormality. In specific embodiments the disorder is a steroid or pituitary hormone disorder, an epinephrine release disorder, a gastrointestinal disorder, a cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, a muscoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder such as, e.g., Alzheimer's disease, a sensory modulation and transmission disorder, a motor coordination disorder, a sensory integration disorder, a motor integration disorder, a dopaminergic function disorder such as, e.g. Parkinson's disease, a sensory transmission disorder, an olfaction disorder, a sympathetic innervation disorder, an affective disorder such as, e.g. depression, a stress-related disorder, a fluid-balance disorder, a urinary disorder such as, e.g., urinary incontinence, a seizure disorder, pain, psychotic behaviour such as, e.g., schizophrenia, morphine or opioid tolerance, opiate addiction or migraine.

More specifically, the compounds of the invention are useful for the treatment or prevention of feeding disorders such as, e.g., overweight, adiposity, obesity and bulimia (e.g. malignant mastocytosis, exogeneous obesity, hyperinsulinar obesity, hyperplasmic obesity, hypophyseal adposity, hypoplasmic obesity, hypophysal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, central obesity etc.), hyperfagia, emotional disorders, dementia or hormonal disorders.

In the present context the term body mass index or BMI is defined as body weight (kg)/height^2 (m^2), and the term overweight is intended to indicate a BMI in a range from about 25 to about 29.9, whereas obesity is intended to indicate a BMI, which is at least about 30.

A compound of the invention is also useful as an agent for preventing or treating lifestyle diseases such as, e.g., diabetes, diabetic complications (e.g. retinopathy, neuropathy, nephropathy etc.), arteriosclerosis and gonitis.

The present invention further relates to a cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound according to the invention

The invention also relates to a method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

A mentioned above, the MCH-related disorders may be a feeding disorder. Accordingly, the invention relates to a method for the treatment and/or prophylaxis of diseases caused by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

The invention also relates to a method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Furthermore, the invention relates to a method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Moreover, the invention relates to a method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Another aspect of the invention is a method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

A still further aspect of the invention is a method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Moreover, the invention relates to a method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to the invention.

Pharmaceutical compositions

The compounds for use in the methods according to the invention are normally presented in the form of a pharmaceutical or a cosmetic composition comprising the specific compound or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

The compounds may be administered to the animal including a mammal such as, e.g., a human by any convenient administration route such as, e.g., the oral, buccal, nasal, ocular, pulmonary, topical, transdermal, vaginal, rectal, ocular, parenteral (including *inter alia* subcutaneous, intramuscular, and intravenous), route in a dose that is effective for the individual purposes. A person skilled in the art will know how to chose a suitable administration route.

The pharmaceutical or cosmetic composition comprising a compound according to the invention may be in the form of a solid, semi-solid or fluid composition.

The solid composition may be in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, granulates, particulate material, solid dispersions or solid solutions.

A semi-solid form of the composition may be a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

The fluid form of the composition may be a solution, an emulsion including nano-emulsions, a suspension, a dispersion, a liposomal composition, a spray, a mixture, a syrup or a aerosol.

Fluid compositions, which are sterile solutions or dispersions can utilized by for example intraveneous, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection of infusion. The compounds may also be prepared as a sterile solid composition, which may be dissolved or dispersed before or at the time of administration using e.g. sterile water, saline or other appropriate sterile injectable medium.

Other suitable dosages forms of the pharmaceutical compositions according to the invention may be vagitories, suppositories, plasters, patches, tablets, capsules, sachets, troches, devices etc.

The dosage form may be designed to release the compound freely or in a controlled manner e.g. with respect to tablets by suitable coatings.

The pharmaceutical composition may comprise a therapeutically effective amount of a compound according to the invention.

The content of a compound of the invention in a pharmaceutical composition of the invention is e.g. from about 0.1 to about 100% w/w of the pharmaceutical composition.

The pharmaceutical or cosmetic compositions may be prepared by any of the method well known to a person skilled in pharmaceutical or cosmetic formulation.

In pharmaceutical or cosmetic compositions, the compounds are normally combined with a pharmaceutical excipient, i.e. a therapeutically inert substance or carrier.

The carrier may take a wide variety of forms depending on the desired dosage form and administration route.

The pharmaceutically or cosmetically acceptable excipients may be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavours, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

Dosage

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the composition, the route of administration, the frequency of administration, the age, weight, gender, diet and condition of the subject to be treated and the condition being treated and the advancement of the disease condition etc.

Suitable dosages may be from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

The amounts can be divided into one or several doses for administration daily, every second day, weekly, every two weeks, monthly or with any other suitable frequency. Normally, the administration is daily.

A compound or a pharmaceutical composition according to the invention may be used in combination with other drug substances such as agents for treating disorders like e.g. diabetes, diabetes complications, obesity, hypertension, hyperlipidemia, arteriosclerosis, arthritis, anxiety, and/or depression etc.

Experimental

Materials and methods

Transfections and Tissue Culture - The cDNA encoding the human MCH-1 receptor was cloned from a human brain cDNA library and cloned into the eukaryotic expression vector pcDNA3.1 (Invitrogen). Assays were performed on transiently transfected COS-7 cells or stably transfected CHO (Chinese Hamster Ovary) cells, expressing the human MCH-1 receptor in pcDNA3.1. Stable MCH-1 receptor transfectants of CHO cells were obtained using 5 μg plasmid cDNA and a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) with subsequent selection in 1 mg/ml G418 (Life Technology). Clones were screened by a MCH receptor radioligand binding assay (as described below). Stably transfected CHO cells were maintained in RPMI 1640 culture medium (Invitrogen), supplemented with 10 % fetal calf serum (Invitrogen), 100 U/ml penicillin, 100 μg/ml streptomycin (Life Technology), and 500 μg/ml G418 (Life Technology). COS-7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 1885 (Invitrogen) supplemented with 10 % fetal calf serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and were transiently transfected by a standard calcium phosphate transfection method (Johansen *et al.*, 1990; Gether *et al.*, 1992) two days before assay.

Radioligand Binding Assay -Transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1 receptor were seeded in multi-well culture plates one day before the assay. The number of cells per well was determined by the apparent expression efficiency of the cell line aiming at 5 - 10 % binding of the added radioligand. Cells were assayed by competition binding for 3 hours at room temperature using 15 pM [^{125}I]-MCH (Amersham Pharmacia Biotech) plus variable amounts of unlabeled ligand in 0.5 ml of a 25 mM Hepes buffer, pH 7.4, supplemented with 10 mM $MgCl_2$, 5 mM $MnCl_2$, 10 mM NaCl, 0.1 % (w/v) bovine serum albumin (BSA), 100 µg/ml bacitracin. The assay was performed in duplicate. Nonspecific binding was determined as the binding in the presence of 1 μM MCH (Bachem). Binding data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego). Values of the dissociation and inhibition constants (K_d and K_i) were estimated from competition binding using the equations $K_d=IC_{50}-L$ and $K_i=IC_{50}/(1+L/K_d)$, respectively, where L is the concentration of radioligand.

Phosphatidylinositol assay - To assay phosphatidylinositol turnover, transiently transfected COS-7 cells or stably transfected CHO cells, expressing human MCH-1

receptor ($2x10^5$ cells/well) were incubated for 24 h with 5 μCi of [^{3}H]-*myo*-inositol (Amersham Pharmacia Biotech) in 0.5 ml inositol-free culture medium. Cells were washed twice in PI-buffer: 20 mM HEPES, pH 7.4, supplemented with 140 mM NaCl, 5 mM KCl, 1 mM $MgSO_4$, 1 mM $CaCl_2$, 10 mM glucose, 0.02% (w/v) bovine serum; and were incubated in 0.5 ml PI-buffer supplemented with 10 mM LiCl at 37 °C for 45 min. Phosphatidylinositol turnover was stimulated by submaximal concentrations of MCH, i.e. 10 nM in the presence of increasing amounts of ligand. The ligand was added 5 min. before adding the agonist (MCH). Cells were extracted with 10 mM ice-cold Formic acid, and the generated [^{3}H]-inositol phosphates were purified on Bio-Rad AG 1-X8 anion-exchange resin. Determinations were made in duplicate. PI data were analyzed and IC_{50} values determined by non-linear regression using the Prism software (GraphPad software, San Diego).

References:

Gether, U., Marray, T., Schwartz, T.W., and Johansen, T.E. (1992). Stable expression of high affinity NK_1 (substance P) and NK_2 (neurokinin A) receptors but low affinity NK_3 (neurokinin B) receptors in transfected CHO cells. *FEBS Lett.*, 296, 241-244.

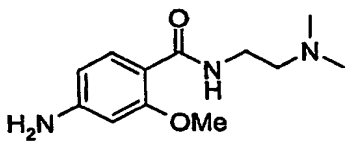
Johansen, T.E., Schøller, M.S., Tolstoy, S. and Schwartz, T.W. (1990). Biosynthesis of peptide precursors and protease inhibitors using new constitutive and inducible eukaryotic expressions vectors. *FEBS Lett.*, 267, 289-294.

Examples

General comments: ^{1}H NMR data are given either in full detailed or with characteristic selected peaks.

Example 1

4-Amino-*N*-(2-dimethylamino-ethyl)-2-methoxy-benzamide



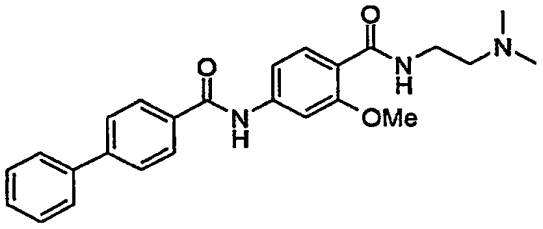
In a flask were placed 4-nitro-2-methoxybenzoic acid (0.50 g, 2.5 mmol) and dichloromethane (10 μl) under nitrogen atmosphere. The solution was cooled to 0°C, whereupon oxalyl chloride (0.20 μl, 2.3 mmol) and *N,N'*-dimethylformamide (2.0 μl) were added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for

1h when potassium carbonate (0.25 g, 2.5 mmol) was added followed by addition of *N,N*-dimethylethylenediamine (0.30 µl , 2.5 mmol). The reaction mixture was stirred overnight before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated leaving 0.54 g (79 %) of *N*-(*N,N*-dimethylaminoethylamine)-4-nitro-2-methoxybenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 6H), 2.52-2.60 (m, 2H), 3.52-3.61 (m, 2H), 4.08 (s, 3H), 7.8-7.95 (m, 2H) and 8.29-8.37 (m, 1H).

To a solution of N-(*N,N*-dimethylaminoethyl)-4-nitro-2-methoxybenzoic amide (0.50 g, 1.87 mmol) in ethanol (10 µl) was Pd/C (40 mg, 20% w/w) added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a pad of celite and the filtrate was concentrated *in vacuo*. The crude product was chromatographed (Al_2O_3, dichloromethane/methanol/ammonia, 200:10:1) giving 0.42 g (95%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 6H), 2.52 (t, 2H), 3.52 (q, 2H), 3.87 (s, 3H), 6.19 (s, 1H), 6.32 (d, 1H), 7.98 (d, 1H) and 8.13 (br s, 1H).

Example 2

Biphenyl-4-carboxylic acid [4-(2-dimethylamino-ethylcarbamoyl)-3-methoxy-phenyl]-amide

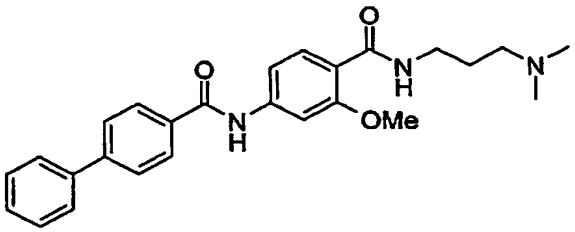


4-phenyl-benzoic acid (0.35 g, 1.8 mmol) was dissolved in dichloromethane (10 µl) in an inert atmosphere and cooled to 0°C, whereupon oxalyl chloride (140 µl,1.6 mmol) and *N,N'*-dimethylformamide (5 µl) were added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 1h when potassium carbonate (0.25 g, 1.77 mmol) was added. This solution was slowly added under inert atmosphere to **Ex 1** dissolved in dichloromethane (5 µl) and the reaction mixture was stirred overnight before extraction with EtOAc and Na2SO4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Al2O3, dichloromethane/methanol/ammonia, 200:10:1, followed by EtOAc/Heptane, 1:1) giving

10 mg (14%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 6H), 4.04 (s, 3H), 6.96 (d, 1H), 8.36 (br s, 1H).

Example 3

Biphenyl-4-carboxylic acid [4-(3-dimethylamino-propylcarbamoyl)-3-methoxy-phenyl]-amide

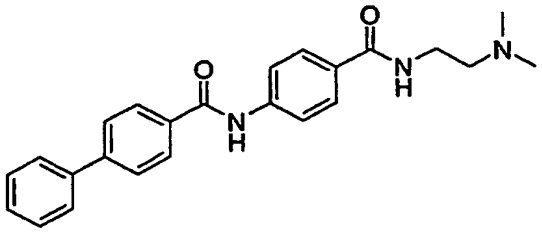


Following the same procedure as described in **Ex 1** was *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide prepared from 2-methoxy-4-nitrobenzoic acid (0.7 g, 3.55 mmol), oxalyl chloride (0.28 μl , 3.2 mmol), triethylamine (0.99 μl, 7.1 mmol) and 3-dimethylaminopropylamine (0.45 μl , 3.55 mmol) followed by reduction with Pd/C (0.04 g, 20% w/w) gave 0.67 g (75%) of *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (t, 2H), 2.24 (s, 6H), 2.36 (t, 2H), 3.49 (m, 2H), 3.90 (s, 3H), 4.02 (br s, 2H), 6.20 (s, 1H), 6.34 (d, 1H), 7.91 (br s, 1H) and 8.02 (d, 1H).

To a solution of 4-biphenylcarbonyl chloride (0.26 g, 0.80 mmol) in dichloromethane (5 μl) under inert atmosphere was a solution of the above prepared compound in dichloromethane (3 μl) added the reaction mixture was stirred at room temperature for three days. The purification was performed according to the protocol for preparation of **Ex 2** and the crude product was chromatographed (Al_2O_3, EtOAc/Heptane, 2:1) giving 0.10 g (30%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): □1.82 (t, 2H), 2.30 (s, 6H), 2.44 (t, 2H), 3.55 (m, 2H), 4.04 (s, 3H), and 6.96 (d, 1H).

Example 4

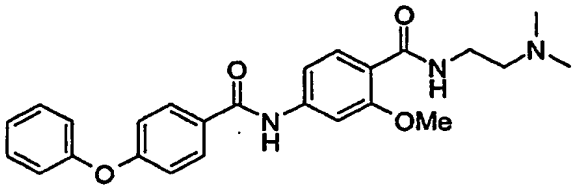
Biphenyl-4-carboxylic acid [4-(2-dimethylamino-ethylcarbamoyl)-phenyl]-amide



To a solution of 4-nitrobenzoyl chloride (0.50 g, 2.7 mmol) in dichloromethane (10 µl) were triethylamine (0.75 µl , 5.4 mmol) and *N,N*-dimethylethyldiamine added. The reaction mixture was stirred for three days before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was dissolved in ethanol (10 µl) and Pd/C (40 mg, 20 % w/w) was added. The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a celite pad and the filtrate was concentrated *in vacuo* giving 0.32 g (56%) of 4-amino-*N*-(*N'*,*N'*-dimethylaminoethyl)benzamide.
To a solution of 4-biphenylcarbonyl chloride (0.47 g, 2.2 mmol) in dichloromethane (6 µl) under inert atmosphere were added triethylamine (0.4 µl , 2.9 mmol) and 4-amino-*N*-(*N'*,*N'*-dimethylaminoethyl)benzamide (0.3 g, 1.45 mmol) dissolved in dichloromethane (3 µl). The reaction mixture was stirred at room temperature for three days. An additional portion of dichloromethane (3 µl) and PS-trisamine (0.8 g, 3.38 mmol/g) were added to the reaction mixture and the stirring was continued for 2 h at room temperature. The resin was filtered off and rinsed twice with dichloromethane (2 x 3 µL) before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Silica, dichloromethane/methanol/ammonia, 100:10:1) and recrystillazed (EtOAc) giving 0.176 g (31%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H), 2.74 (t, 2H), 4.19 (t, 2H), 7.90 (d, 2H).

Example 5

***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide**

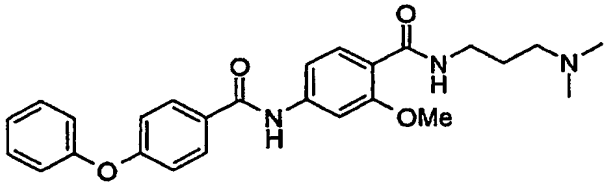


In a flask were placed 4-phenoxy benzoic acid (27 mg, 0.13 mmol) and *N,N*-dimethylformamide (2 µL) and the flask was cooled to 0°C, whereupon EDAC (24 mg,

0.13 mmol) and HOBt (17 mg, 0.13 mmol) were added. The mixture was gently stirred for 20 minutes at room temperature before **Ex 1** (41 mg, 0.19 mmol) dissolved in *N,N*-dimethylformamide and DiPEA (22 µl, 0.13 mmol) were added. The reaction was continuously stirred three days before extraction with EtOAc and Na_2SO_4 (aq) was performed. The combined organic phases were dried, filtrated and evaporated. The crude product was chromatographed (Silica, dichloromethane/methanol/ammonia, 100:20:2) yielded 12 mg (20%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 6H), 2.77 (m, 2H), 3.68 (m, 2H), 4.03 (s, 3H), 8.16 (d, 1H), and 8.39 (br s, 1H).

Example 6

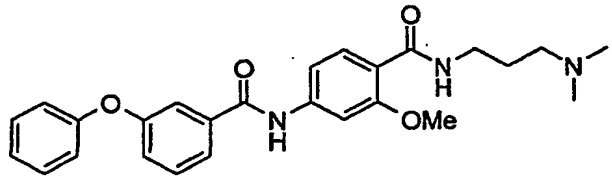
***N*-(3-Dimethylamino-propyl)-2-methoxy-4-(4-phenoxy-benzoylamino)-benzamide**



N-(N,N-dimethylaminopropyl)-4-amino-2-methoxybenzamide was prepared according to the experiment described in **Ex 3**. In a flask were placed PS-DCC (1.2 g, 1.35 mmol/g), dichloromethane (15 µL), 4-phenoxy benzoic acid (0.26 g, 1.2 mmol) and HOBt (0.18 g, 1.35 mmol) and the mixture was gently stirred for 10 minutes before *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide (0.20g, 0.80 mmol) was added. The reaction was stirred for three days when PS-trisamine (1.0 g, 3.38 mmol/g) was added. After 2h the resins were filtered off and rinsed with dichloromethane (20 µL). The solvent was removed under vacuum giving the crude product. Chromatography (Silica, dichloromethane/methanol/ammonia, 200:10:1) yielded 8 mg (2%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.8 (dt, 2H), 2.28 (s, 3H), 2.42 (t, 2H), 3.53 (q, 2H), 4.02 (s, 3H), 6.91 (d, 1H) and 7.89 (d, 2H).

Example 7

***N*-(3-Dimethylamino-propyl)-2-methoxy-4-(3-phenoxy-benzoylamino)-benzamide**

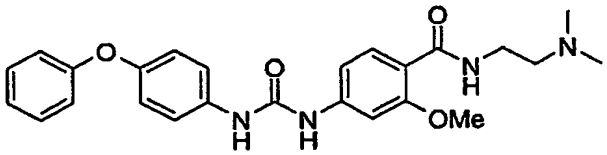


N-(N,N)-dimethylaminopropyl)-4-amino-2-methoxybenzamide was prepared according to the experiment described in **Ex 3**. In a flask were placed PS-DCC (1.2 g, 1.35 mmol/g),

dichloromethane (15 µL), 3-phenoxybenzoic acid (0.26 g, 1.2 mmol) and HOBt (0.18 g, 1.35 mmol) and the mixture was gently stirred for 10 minutes before *N-(N,N*-dimethylaminopropyl)-4-amino-2-methoxybenzamide (0.20g, 0.80 mmol) was added. The reaction was stirred for three days when PS-trisamine (1.0 g, 3.38 mmol/g) was added. After 2h the resins were filtered off and rinsed with dichloromethane (20 µL). The solvent was removed under vacuum giving the crude product. Chromatography (Silica, dichloromethane/methanol/ammonia, 100:20:2) yielded 11 mg (3%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (dt, 2H), 2.28 (s, 3H), 2.42 (t, 2H), 3.54 (m, 2H), 4.00 (s, 3H), 6.92 (d, 1H) and 7.99 (d, 1H).

Example 8

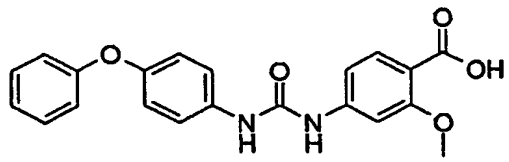
***N*-(2-Dimethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



To a solution of **Ex 1** (30 mg, 0.13 mmol) in dichloromethane (2 µL) under nitrogen atmosphere was 4-phenoxyphenylisocyanate (64 µl, 0.30 mmol) added. The reaction was stirred for 2 h at room temperature, whereupon PS-trisamine (100 mg, 4.2 mmol/g). The suspension was gentle stirred over night. Methanol (20 µL) was added to dissolve some precipitation before the resin was filtered off and rinsed with dichloromethane (10 µL). The solvents were removed in vacuo and the crude product was purified through chromatography (silica, dichloromethane/ methanol/ammonia, 100:20:2) giving 24 mg (42%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (t, 2H), 3.54 (m, 2H), 3.90 (s, 3H), 8.52 (s, 1H), 8.67 (s, 1H).

Example 9

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzoic acid

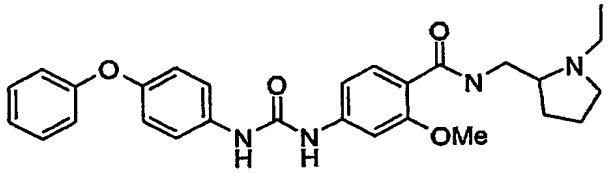


To a solution of 4-nitro-2-methoxybenzoic acid (5.0g, mmol) in ethanol (100 µL) was added Pd/C (200 mg, 20% w/w). The reaction mixture was stirred at room temperature under a hydrogen atmosphere over night. The catalyst was filtered off through a pad of celite and the filtrate was concentrated *in vacuo* giving 4-amino-2-methoxybenzoic acid.

To a solution of 4-amino-2-methoxybenzoic acid (0.50 g, 3.0 mmol) in dichloromethane (10 μL) was added 4-phenoxyphenylisocyanate (0.65 μL, 3.6 mmol) under inert atmosphere. The reaction mixture was stirred for three days at room temperature and a precipitate was formed. Filtration gave 1.1 g (97%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.92-7.02 (m, 5H), 7.09 (t, 1H), 7.32-7.42 (m, 3H), 7.48 (d, 2H), 7.66 (d, 1H), 8.79 (s, 1H), and 9.03 (s, 1H).

Example 10

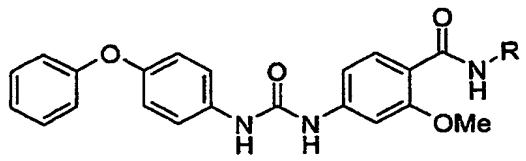
***N*-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**



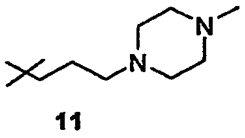
In a flask were placed **Ex 9** (57 mg, 0.15 mmol), HOBt (23 mg, 0.17 mmol), PS-DCC (0.15 g, 1.35 mmol/g), and dichloromethane (2 μL). The mixture was stirred at room temperature for 30 minutes, whereupon 2-aminomethyl-ethylpyrrolidine (0.10 mmol) was added. The reaction mixture was stirred over night. PS-trisamine (140 mg, 0.50 mmol) was added and stirring was continued for a day more. The resin was filtered off and rinsed with dichloromethane (3 x 2 μL). The solvent was removed *in vacuo* giving 35 mg (71%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, 3H), 3.88 (s, 3H), 6.69 (d, 1H), 8.63 (t, 1H), 8.82 (s, 1H), 9.12 (s, 1H).

Example 11-18

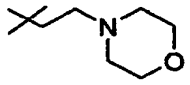
According to the procedure outlined in example 10 were the following compounds prepared utilizing **Ex 9** and the corresponding primary amines to the R-group;



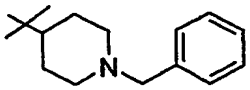
R =



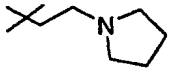
11



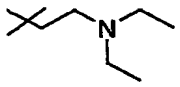
14



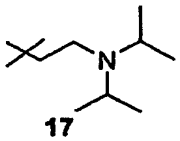
16



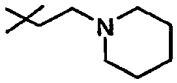
12



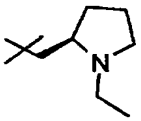
15



17



13



18

Example 11

2-Methoxy-N-[3-(4-methyl-piperazin-1-yl)-propyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Ex 9 and 1-(3-aminopropyl)-4-methylpiperazine was coupled giving 43 mg (82%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.60 (d, 1H), 8.69 (s, 1H), 9.02 (s, 1H).

Example 12

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-benzamide

Ex 9 and *N*-(2-aminoethyl)pyrrolidine was coupled giving 30 mg (63%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.72 (d, 1H), 8.44 (t, 1H), 8.85 (s, 1H), 9.13 (s, 1H).

Example 13

2-Methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-N-(2-piperidin-1-yl-ethyl)-benzamide

Ex 9 and 1-(2-aminoethyl)piperidine was coupled giving 40 mg (81%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.64 (d, 1H), 7.06 (t, 1H), 7.95 (d, 1H), 8.58 (t, 1H), 8.76 (s, 1H), 9.03 (s, 1H).

Example 14

2-Methoxy-*N*-(2-morpholin-4-yl-ethyl)-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Ex 9 and 4-(2-aminoethyl)morpholine was coupled giving 18 mg (36%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 3H), 6.47 (d, 1H), 7.08 (t, 1H), 8.47 (s, 1H), 8.58 (t, 1H), 8.74 (s, 1H).

Example 15

***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Ex 9 and *N,N*-diethyl-ethylendiamine was coupled giving 38 mg (78%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, 6H), 2.70 (q, 4H), 3.86 (s, 3H), 6.73 (d, 1H), 7.05 (t, 1H), 8.55 (t, 1H), 8.89 (s, 1H), 9.19 (s, 1H).

Example 16

N-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Ex 9 and 4-amino-1-benzylpiperidine was coupled giving 39 mg (70%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (s, 2H), 3.91 (s, 3H), 8.51 (s, 1H), 8.76 (s, 1H).

Example 17

***N*-(2-Diisopropylamino-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H), 8.82 (s, 1H), 9.09 (s, 1H).

Example 18

***N*-(1-Ethyl-pyrrolidin-2*R*-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Ex 9 and (*R*)-2-aminomethyl-ethylpyrrolidine was coupled giving 35 mg (71%) of the title product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, 3H), 3.88 (s, 3H), 6.69 (d, 1H), 8.63 (t, 1H), 8.82 (s, 1H), 9.12 (s, 1H).

The following examples were prepared from **Ex 9** according to the same procedure as Ex 10-18

Example 19
***N*-(4-Benzyl-morpholin-2-ylmethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.49 (dd, 1H), 7.96 (d, 1H), 8.42 (t, 1H), 8.56 (s, 1H), 8.82 (s, 1H).

Example 20
***N*-(1-Benzyl-pyrrolidin-3-yl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 6.48 (dd, 1H), 8.40 (d, 1H), 8.60 (s, 1H), 8.87 (s, 1H).

Example 21
***N*-(2-Diethylamino-1-methyl-ethyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, 6H), 3.84 (s, 3H), 9.51 (s, 1H), 9.88 (s, 1H).

Example 22
***N*-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.50 (dd, 1H), 8.65-8.70 (m, 2H), 8.56 (s, 1H).

Example 23
2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Example 24
2-Methoxy-*N*-[3-(2-methyl-piperidin-1-yl)-propyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Example 25

***N*-(3-Diethylamino-propyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

Example 26

2-Methoxy-*N*-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide

Example 27

***N*-(3-Dibutylamino-propyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 6H), 3.87 (t, 3H), 8.21 (t, 1H), 9.17 (s, 1H), 9.53 (s, 1H).

Example 28

***N*-(4-Dimethylamino-phenyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

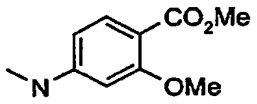
Example 29

***N*-(3-Dimethylamino-phenyl)-2-methoxy-4-[3-(4-phenoxy-phenyl)-ureido]-benzamide**

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.85 (s, 6H), 4.08 (s, 3H), 9.90 (s, 1H).

Example 30

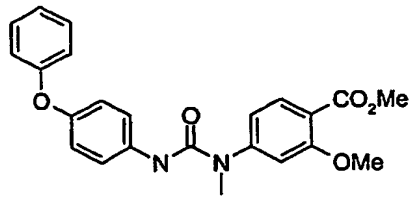
2-Methoxy-4-methylamino-benzoic acid methyl ester



A solution of sodium methoxide (0.745g, 13.8 mmol), paraformaldehyde (0.124g, 4.14 mmol) and methyl 4-amino-2-methoxybenzoate (050g, 2.76 mmol) in methanol (40μL) was stirred overnight at 40°C before sodium borohydride (0.229g, 6.07 mmol) was added at room temperature. The resulting mixture was heated at 50°C for 8 hours. Methanol was removed *in vacuo*. The residue was partitioned between saturated aqueous NaHCO3 and dichloromethane. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3x). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo* to give a crude solid which was chromatographed over silica gel (CH_2Cl_2/MeOH/NH_3 : 95/4.5/0.5) to give the title compound as a white solid (0.278g, 1.43 mmol, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.88 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.30 (bs, 1H), 6.07 (s, 1H), 6.14 (d, 1H), 7.76 (d, 1H)

Example 31

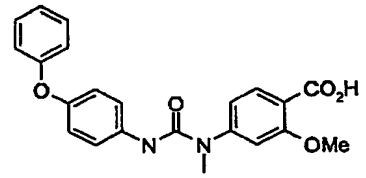
2-Methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzoic acid methyl ester



The title compound **Ex 31** was obtained by carrying out the same procedure as in Example 8, using **Ex 30** and commercially available 4-phenoxyphenylisocyanate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36 (s, 3H), 3.91 (s, 6H), 6.35 (s, 1H), 6.93-7.26 (m, 11H), 7.88 (d, 1H)

Example 32

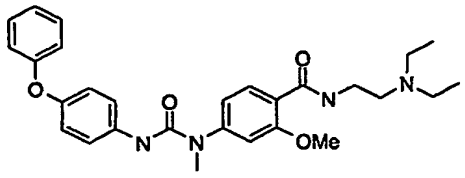
2-Methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzoic acid



A solution of **Ex 31** (0.38g, 0.93 mmol) and lithium hydroxide (0.034g, 1.4mmol) in a THF/water mixture (2/1, 6μL) was stirred at 30°C for 3 days. After removal of the solvent *in vacuo*, the residue was diluted with water and washed with dichloromethane. The aqueous phase was then saturated with solid sodium chloride and acidified to pH = 1 with a 6N aq. HCl solution. The aqueous phase was extracted with dichloromethane. The organic phases were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **Ex 32** as a white solid (0.249g, 0.63mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (s, 3H), 4.09 (s, 3H), 6.52 (s, 1H), 6.93-7.33 (m, 11H), 8.20 (d, 1H)

Example 33

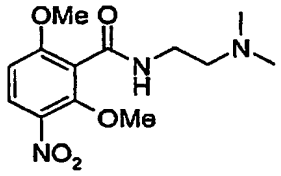
***N*-(2-Diethylamino-ethyl)-2-methoxy-4-[1-methyl-3-(4-phenoxy-phenyl)-ureido]-benzamide**



A solution of compound **Ex 32** (0.02g, 0.051mmol), EDAC (0.0146g, 0.076mmol) and HOBt (0.0089g, 0.066mmol) in dichloromethane (3μL) was stirred at RT for 5 minutes before N,N-diethylethylenediamine (0.0086μL) was added. The resulting reaction mixture was stirred at RT overnight, washed with saturated aq. NaHCO3 solution (3x), brine, dried over MgSO4 and concentrated *in vacuo*. The crude was chromatographed over silica gel (CH_2Cl_2/MeOH/NH_3 : 90/9/1) to give the title compound as a colourless oil which crystallised upon standing (0.025g, 0.051mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, 6H), 2.58 (q, 4H), 2.66 (t, 2H), 3.36 (s, 3H), 3.54 (m, 2H), 3.97 (s, 3H), 6.36 (s, 1H), 6.91-7.32 (m, 11H), 8.29 (d, 1H), 8.35 (bs, 1H)

Example 34

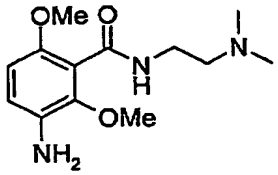
***N*-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-nitro-benzamide**



A flask was charged with 2,6-dimethoxy-3-nitrobenzoic acid (1 g, 4.4 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.27 g, 6.6 mmol), hydroxybenzotriazole (772 mg, 5.72 mmol) and N,N-dimethylethylene diamine (0.48 μL, 4.4 mmol). Dichloromethane (50 μL) was added and the suspension was stirred under air for 16 h. The now clear reaction mixture was washed consecutively with water (2 x 20 μL) and brine (1 x 20 μL). The organic solution was then briefly dried over sodium sulfate before being filtered and reduced *in vacuo* to give *N*-(*N,N*-dimethylaminoethylamine)-2,6-dimethoxy-3-nitrobenzamide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04-7.99 (2H, d), 6.77-6.72 (2H, d), 6.50-6.30 (1H, br s, NH), 3.97 (3H, s, MeO), 3.92 (3H, s, MeO), 3.60-3.45 (2H, m), 2.55-2.45 (2H, m), 2.25 (6H, s, Me_2N).

Example 35

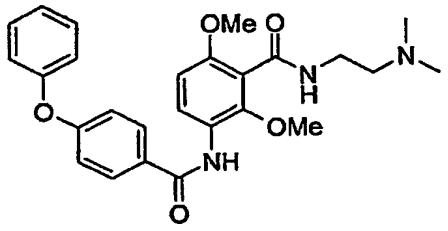
3-Amino-*N*-(2-dimethylamino-ethyl)-2,6-dimethoxy-benzamide



To a solution of *N*-(*N,N*-dimethylaminoethylamine)-2,6-dimethoxy-3-nitrobenzamide (1.31 g, 4.4 mmol) in dry methanol (50 μL) was added 10% palladium on carbon (50 mg). The reaction vessel was sealed and the atmosphere exchanged with nitrogen. The solution was then vigorously stirred and the atmosphere exchanged with hydrogen via a double balloon. Stirring continued for 16 h before the ballon was removed and the reaction mixture was filtered through a plug of celite (approx. 10 g). The residues were washed with excess methanol (approx. 100 μL) and the combined filtrates were reduced *in vacuo* returning a crude product which was chromatographed (Al_2O_3, dichloromethane-/methanol/triethylamine, 90:9:1) to give *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99-7.91 (1H, m), 6.72-6.67 (1H, m), 3.88 (3H, s, MeO), 3.85 (3H, s, MeO), 3.72-3.67 (2H, m), 3.13-3.05 (2H, m), 2.72 (6H, s, Me_2N).

Example 36

***N*-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-(4-phenoxy-benzoylamino)-benzamide**

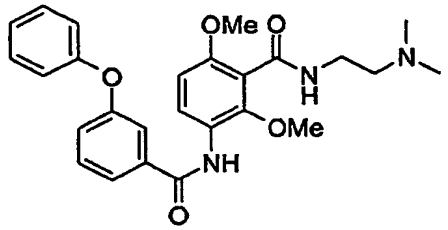


A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (8 mg, 32 □mol), hydroxybenzotriazole (5.6 mg, 46 □mol), *N,N*-dimethylaminopyridine (1 crystal) and 4-phenoxybenzoic acid (6.8 mg, 32 □mol). Dichloromethane (10 μL) was added and the solution was stirred under air before PS-DCC (60 mg, approx. 64 □mol) was added. Stirring continued for 72 h before PS-trisamine (200 mg) was added and the resulting suspension stirred for 3 h. The resins were removed by filtration and further washed with dichloromethane (50 μL) and the combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title product.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45-8.38 (1H, d), 8.40-8.30 (1H, br s, NH), 7.60-7.30 (5H, m), 7.22-7.12 (2H, m), 7.08-7.00 (1H, d), 6.74-6.55 (1H, d), 6.52-6.48 (2H, m, Ar-H + NH), 3.89 (3H, MeO), 3.83 (3H, MeO), 3.58-3.52 (2H, m), 2.54-2.48 (2H, m), 2.26 (6H, s, Me_2N).

Example 37

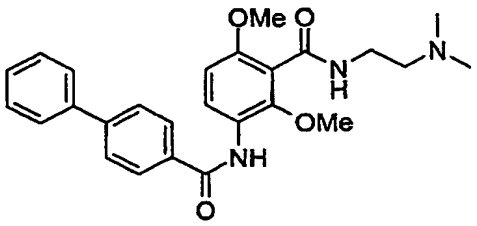
***N*-(2-Dimethylamino-ethyl)-2,6-dimethoxy-3-(3-phenoxy-benzoylamino)-benzamide**



A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (80 mg, 0.32 mmol), hydroxybenzotriazole (43 mg, 0.32 mmol), *N,N*-dimethylaminopyridine (1 crystal) and 3-phenoxybenzoic acid (79 mg, 0.40 mmol). Dichloromethane (8 µL) was added and the solution was stirred under air before PS-DCC (350 mg, approx. 0.64 mmol) was added. Stirring continued for 72 h. Then PS-trisamine (100 mg) was added and stirred for 1 h before PS-iscocyanate (100 mg) was added and the resulting suspension stirred for a futher 1 h. The resins were removed by filtration and further washed with dichloromethane (50 µL) and the combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42-8-38 (1H, d), 8.35-8.28 (1H, br s, NH), 7.48-7.35 (5H, m), 7.25-7.10 (2H, m), 7.08-7.10 (2H, d), 6.75-7.69 (1H, d), 6.68-6.48 (1H, br s, NH), 3.89 (3H, s, MeO), 3.83 (3H, s, MeO), 3.58-3.52 (2H, m), 2.53-2.49 (2H, m), 2.25 (6H, s, Me_2N).

Example 38

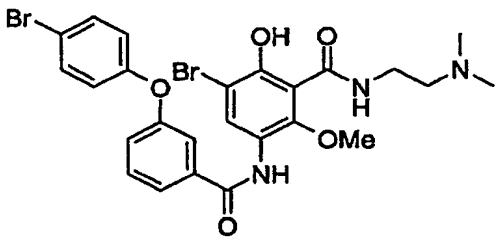
Biphenyl-4-carboxylic acid [3-(2-dimethylamino-ethylcarbamoyl)-2,4-dimethoxy-phenyl]-amide



A flask was charged with *N*-(*N,N*-dimethylaminoethylamine)-3-amino-2,6-dimethoxybenzamide (80 mg, 0.32 mmol), hydroxybenzotriazole (43 mg, 0.32 mmol), *N,N*-dimethylaminopyridine (1 crystal) and biphenylacetic acid (79 mg, 0.40 mmol). Dichloromethane (8 μL) was added and the solution was stirred under air before PS-DCC (350 mg, approx. 0.64 mmol) was added. Stirring continued for 72 h. Then PS-trisamine (100 mg) was added and stirred for 1 h before PS-iscocyanate (100 mg) was added and the resulting suspension stirred for a futher 1 h. The resins were removed by filtration and further washed with dichloromethane (50 μL) and the combined organics were reduced *in vacuo* to give crude material which was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55-8.45 (1H, d), 8.45-8.35 (1H, br s, NH), 7.97-7.95 (2H, d), 7.80-7.70 (2H, d), 7.70-7.60 (2H, d), 7.60-7.40 (3H, m), 6.76-6.73 (1H, d), 6.60-6.50 (1H, br s, NH), 3.67 (3H, s, MeO), 3.86 (3H, s, MeO), 3.61-3.55 (2H, m), 256-2.52 (2H, m), 2.28 (6H, s, Me_2N); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 165.1, 153.6, 147.8, 140.3, 134.0, 129.4, 128.5, 127.9, 127.6, 125.5, 122.4, 120.4, 120.4, 107.3, 62.7, 58.0, 56.6, 46.3, 45.5, 37.7.

Example 39

3-Bromo-5-[3-(4-bromo-phenoxy)-benzoylamino]-*N*-(2-dimethylamino-ethyl)-2,6-dimethoxy-benzamide

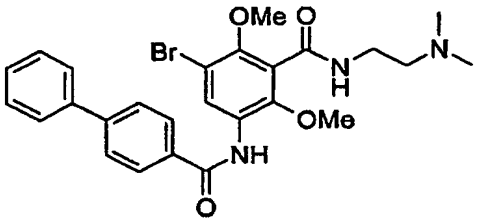


To a solution of **Ex 37** (120 mg, 0.26 mmol) in dichloromethane (10 μL) with acetic acid (1 drop) was added bromine (27 □L, 0.52 mmol) dropwise. The brown solution was then stirred for 16 h before a saturated solution of sodium thiosulfate (10 μL) was added and shaken to remove excess bromine. The organic solution was further washed with water (10 μL) and brine (10 μL) before being dried over sodium sulphate, filtered and reduced *in*

vacuo. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$ δ 9.10-9.00 (1H, br app s, NH), 8.88 (1H, s), 8.60-8.50 (1H, br s, NH), 7.64-7.60 (1H, dt), 7.57-7.56 (1H, t), 7.53-7.45 (3H, m), 7.21-7.18 (1H, dd), 6.98-6.93 (2H, d), 3.89 (3H, s, MeO), 3.58-3.53 (2H, q, CH_2NH), 2.59-2.57 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 40

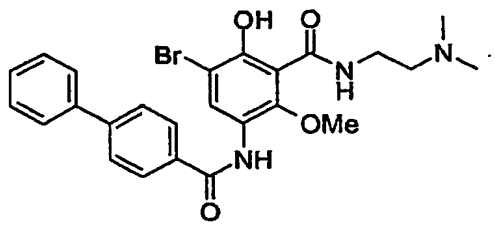
Biphenyl-4-carboxylic acid [5-bromo-3-(2-dimethylamino-ethylcarbamoyl)-2,4-dimethoxy-phenyl]-amide



To a solution of **Ex 38** (120 mg, 0.26 mmol) in dichloromethane (10 μL) with acetic acid (1 drop) was added bromine (27 μL, 0.52 mmol) dropwise. The brown solution was then stirred for 16 h before a saturated solution of sodium thiosulfate (10 μL) was added and shaken to remove excess bromine. The organic solution was further washed with water (10 μL) and brine (10 μL) before being dried over sodium sulphate, filtered and reduced *in vacuo*. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 90:9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$ δ 8.82 (1H, s), 8.50-8.60 (1H, br s, NH), 7.98-7.93 (2H, d), 7.77-7.72 (2H, d), 7.67-7.62 (2H, m), 7.58-7.35 (3H, m), 6.92-6.80 (1H, br s, NH), 3.96 (3H, s, MeO), 3.89 (3H, s, MeO), 3.64-3.59 (2H, q, CH_2NH), 2.65-2.58 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 41

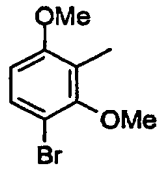
Biphenyl-4-carboxylic acid [5-bromo-3-(2-dimethylamino-ethylcarbamoyl)-4-hydroxy-2-methoxy-phenyl]-amide



From the above reaction a second product was isolated and identified as **Ex 41**. ^{1}H NMR (300 MHz, $CDCl_3$ δ 9.07-9.04 (1H, br s, NH), 8.96 (1H, s), 8.75-8.65 (1H, br s, NH), 8.02-7.99 (2H, d), 7.76-7.73 (2H, d), 7.68-7.65 (2H, d), 7.60-7.35 (3H, m), 3.90 (3H, s, MeO), 3.59-3.54 (2H, q, CH_2NH), 2.58-2.54 (2H, t, CH_2N), 2.32 (6H, s, Me_2N).

Example 42

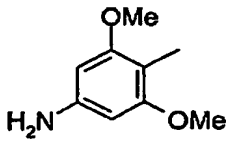
1-Bromo-2,4-dimethoxy-3-methyl-benzene



To a solution of 2,6-dimethoxytoluene (5 g, 33 mmol) in dichloromethane (100 µL) and acetic acid (1 drop) held at 0°C was added bromine (1.67 µL, 33 mmol) dropwise. The pale brown solution was stirred for a further 5 h before being washed with a saturated solution of sodium thiosulfate (20 µL), sodium bicarbonate (20 µL), water (20 µL) and brine (20 µL). The organic solution was then dried over sodium thiosulfate, filtered and evaporated *in vacuo* to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.35-7.32 (1H, d), 6.56-6.53 (1H, d), 3.82 (3H, s, MeO), 3.81 (3H, s, MeO), 2.22 (3H, s, CH_3).

Example 43

3,5-Dimethoxy-4-methyl-phenylamine

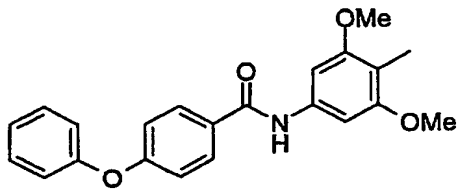


To a freshly prepared suspension of potassium amide (from potassium 12.87 g, 330 mmol) in liquid ammonia (300 µL) held at -78°C was added *example 9* (7.6 g, 33 mmol) dropwise over twenty minutes. The resulting suspension was stirred for a further 3 h and then excess potassium amide was quenched carefully with solid ammonium chloride (10 g) added portionwise over thirty minutes. Toluene (200 µL) was added and the liquid ammonia allowed to evaporate. The organic solution was then washed with water (3 x 100 µL) before being shaken with hydrochloric acid (6 N, 200 µL). The nascent precipitate was then collected by filtration and further washed with water (100 µL). The

residue was stirred with sodium hydroxide (10 N, 100 µL) for 1 h to form the free aniline, which was collected by filtration. The residues were washed with water (3 x 20 µL) and dried *in vacuo* to give the title compound.

Example 44

***N*-(3,5-Dimethoxy-4-methyl-phenyl)-4-phenoxy-benzamide**



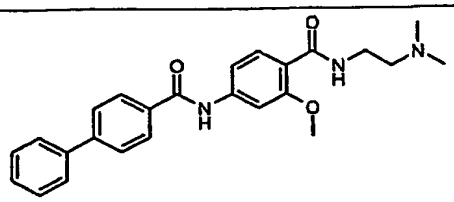
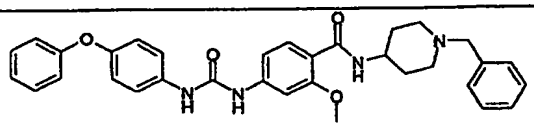
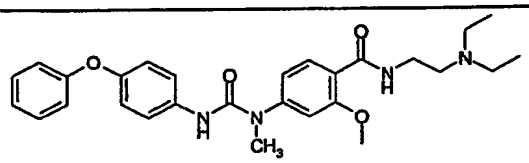
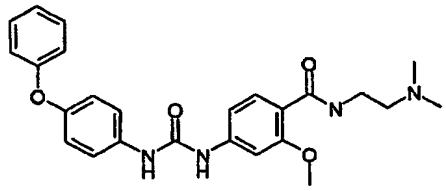
A flask was charged with **Ex 43** (334 mg, 2 mmol), 4-phenoxybenzoic acid (471 mg, 2.2 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (573 m g, 3 mmol) and hydroxybenzotriazole (351 mg, 2.6 mmol). Dichloromethane (20 µL) was added and the suspension was stirred for 100 h. The now clear solution was washed with hydrochloric acid (1 N, 20 µL), sodium bicarbonate (20) and water (20 µL). The organic solution was dried over sodium sulphate, filtered and reduced *in vacuo*. The crude material was chromatographed (Al_2O_3, dichloromethane/methanol/triethylamine, 98:1:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.88-7.85 (2H, d), 7.75 (1H, s), 7.50-7.40 (2H, m), 7.25-7.15 (1H, m), 7.12-7.05 (4H, m), 6.93 (2H, s), 5.95 (1H, s), 3.85 (6H, s, MeO), 2.09 (3H, s, CH_3).

Example 45

***In vitro* tests of compounds according to the invention**

The following results were obtained

Receptor binding data

Compound	Example	Receptor binding IC_{50} µM	IP3 IC_{50} µM
	**Ex 2**	1.48	
	**Ex 16**	0.22	1.8
	**Ex 33**	0.048	0.29
	**Ex 8**	0.38	2.3

The following compounds are prepared as described in previous examples.

N-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-(3-phenyl-ureido)-benzamide
N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-chloro-phenyl)-ureido]-2-methoxy-benzamide
4-[3-(3-Chloro-phenyl)-ureido]-*N*-(2-dimethylamino-ethyl)-2-methoxy-benzamide
N-(2-Dimethylamino-ethyl)-2-methoxy-4-(3-phenyl-ureido)-benzamide
N-(2-Diethylamino-ethyl)-2-methoxy-4-(3-phenyl-ureido)-benzamide
4-[3-(3-Chloro-phenyl)-ureido]-*N*-(2-diethylamino-ethyl)-2-methoxy-benzamide
N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide
N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide
N-{3-[4-(4-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide

N-{3-[4-(3-Acetylamino-phenyl)-piperidin-1-yl]-propyl}-2-methoxy-4-(3-phenyl-ureido)-benzamide

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-(3-phenyl-ureido)-benzamide

2-Methoxy-*N*-(3-morpholin-4-yl-propyl)-4-(3-phenyl-1-methyl-ureido)-benzamide

4-[3-(4-Chloro-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(4-Chloro-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

2-Methoxy-4-[3-(4-methoxy-phenyl)-ureido]-*N*-(3-morpholin-4-yl-propyl)-benzamide

2-Methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Chloro-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Chloro-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Iodo-phenyl)-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

4-[3-(3-Iodo-phenyl)-1-methyl-ureido]-2-methoxy-*N*-(3-morpholin-4-yl-propyl)-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(4-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-benzamide

N-(1-Benzyl-piperidin-4-yl)-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-iodo-phenyl)-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-[3-(3-iodo-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-(3-phenyl-ureido)-2-methoxy-benzamide

N-(1-Benzyl-piperidin-4-yl)-4-(3-phenyl-1-methyl-ureido)-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-iodo-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-iodo-phenyl)-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(3-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-methoxy-phenyl)-1-methyl-ureido]-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-[3-(4-methoxy-phenyl)-ureido]-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(4-chloro-phenyl)-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-4-[3-(4-chloro-phenyl)-1-methyl-ureido]-2-methoxy-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-(1-methyl-3-phenyl-ureido)-benzamide

N-[2-(4-Benzyl-piperazin-1-yl)-ethyl]-2-methoxy-4-(3-phenyl-ureido)-benzamide

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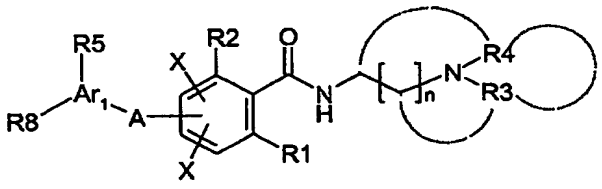
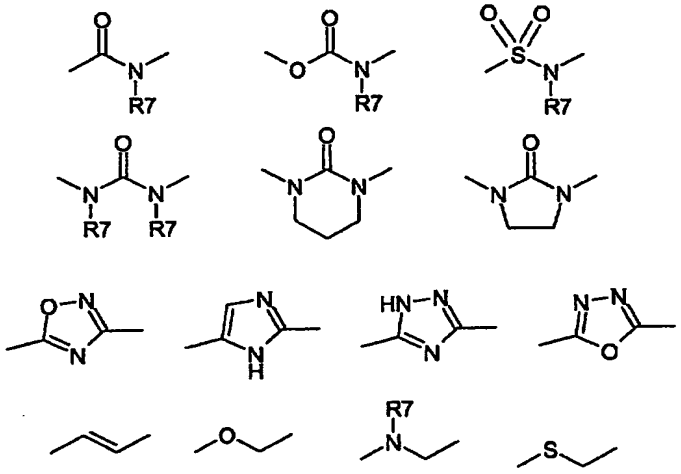
CLAIMS

1. A compound with the following structure (Formula I)



wherein -A- is a linker, which is selected from the group consisting of



and, wherein the linker may be attached via either of the two free bonds to the Ar1 group;

and R7 is the same or different and is hydrogen or a straight or branched C_1-C_4 alkyl or alkenyl group;

Ar_1 is a aryl or heteroaryl group such as, e.g. phenyl, pyridine, pyrimidine, pyrazine, thiophene, oxazole, isothiazole, pyrazole, pyrrole, imidazole, indole, benzimidazole, quinoline, isoquinoline, furan, benzofuran, benzothiophene, benzothiazole, indazole, thiazole, isoxazole, oxadiazole, indan;

R1 is a lower alkoxy group alkyl-O- with one to four carbon atoms and preferably one carbon;

R2 is an R1 group or a hydrogen, OH or NH_2 group;

R3 and R4 are the same or different selected from straight or branched alkyl, alkenyl or alkynyl groups with 1-8 carbon atoms; cycloalkyl groups with 3-7 carbons; alkylcycloalkyl with 4-9 carbons atoms; alkylaryl groups such as benzyl, 2-ethylphenyl, 3-propylphenyl, 4-butylphenyl; alkylheterocyclyl groups such as 2-ethylpiperazine, 3-propylpiperidine; alkylheteroaryl groups; the aryl, heterocyclyl and heteroaryl groups may be substituted with substituents such as Alk-CONH-, Alk-O-, HO-, NC-, AlkNH-, Alk_2N-, $-CONH_2$, -CONHAlk, $-CONAlk_2$, aryl, substituted aryl, benzyl, substituted benzyl groups;

Alk is the same or a different alkyl, alkenyl or alkynyl group;

R3 or R4 may optionally be linked to each other, when possible, as indicated in Formula I; and oxygen or nitrogen atoms may be inserted in the chain or ring in a chemically stable position;

R5 may the same or different selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), hydroxy, alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), hydroxylalkyl groups, carboxamido groups ($-CONH_2$, -CONHAlk, $-CONAlk_2$), acylamido groups (-NHCO-Alk), acyl groups (-CO-Alk), -CHO, nitrile, alkyl, alkenyl or alkynyl groups, $-CF_3$, $-OCF_3$, $-SCF_3$, $-SCH_3$, $-SO_2NH_2$, $-SO_2NHAlk$, $-SO_2NAlk_2$, $-SO_2Alk$;

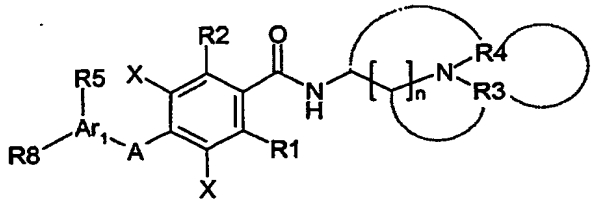
R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, aryl groups (Ar), heteroaryl groups, heterocyclyl groups, alkylcycloalkyl groups, alkylaryl groups, alkylheterocyclyl groups, alkylheteroaryl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -CONHAr -$CONAlk_2$, -NHCO-Alk, -NHCO-Ar, -CO-Alk, -CO-Ar, $-CF_3$, $-OCF_3$, $-SCF_3$, $-SCH_3$;

more than one R5 group, same or different, or more than one R8 group, same or different, may be present on Ar1; when more than one R5 and R8 group are present they could be connected to each other to form rings;

X being the same or different H, F, Cl, Br, I, CF_3, OCF_3, SCF_3, SCH_3, OCH_3 or lower alkyl or alkenyl group;

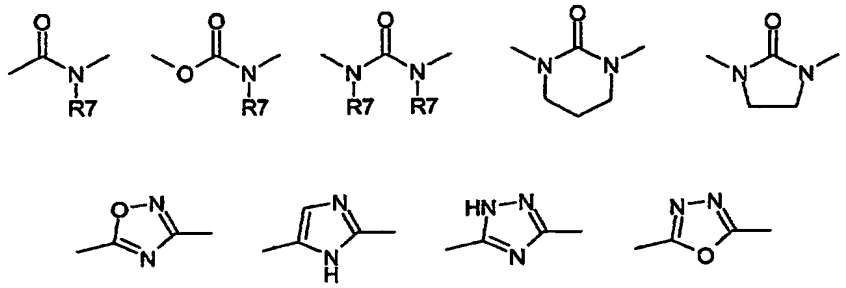
n is 1,2 or 3.

2. A compound according to claim 1 with the following structure (Formula Ia)

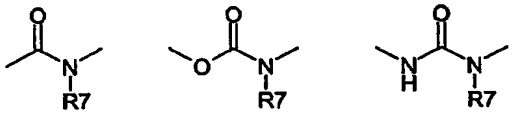


wherein Ar_1, A, B, R1, R2, R3, R4, R5, R8, n and X are as defined in claim 1.

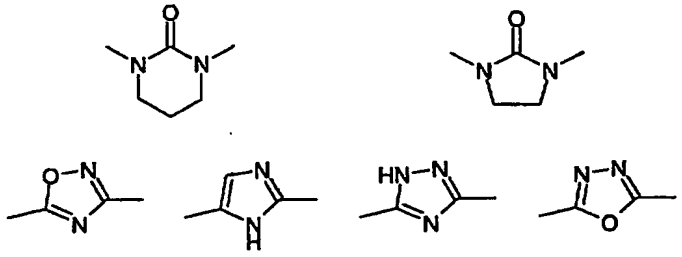
3. A compound according to claim 1 or 2, wherein -A- is selected from the group consisting of



4. A compound according to any of the preceding claims, wherein the –A- moiety is selected from the group consisting of



5. A compound according to any of claims 1-3, wherein the –A- moiety is selected from the group consisting of



6. A compound according any of the preceding claims, wherein R8 is halogen atoms, alkyl, alkenyl or alkynyl groups, cycloalkyl groups with 3-7 carbons, alkylcycloalkyl groups, alkoxy groups (AlkO-), dialkylamino groups (Alk_2N-), -CONHAlk, -$CONAlk_2$, -NHCO-Alk, -CO-Alk, -CF_3, -OCF_3, -SCF_3, -SCH_3.

7. A compound according to any of claims 1-5, wherein R8 is aryl groups (Ar), heterocyclyl groups, heteroaryl groups, alkylaryl groups, alkylheteroaryl groups, alkylheterocyclyl groups, arylalkoxy groups (e.g. $ArCH_2O$-), aryloxy groups (ArO-), -CONHAr, -NHCO-Ar, or -CO-Ar.

8. A compound according to any of the preceding claims, wherein Ar_1 is an aryl, heterocyclyl or heteroaryl group such as, e.g. phenyl, pyridine, thiophene.

9. A compound according to any of the preceding claims, wherein R2 is hydrogen.

10. A compound according to any of the preceding claims, wherein R2 is hydrogen and X is F, Cl, Br, I, CF_3, OCF_3, OCH_3, SCF_3, SCH_3 or Alk.

11. A compound according to any of claims 1-8, wherein R2 is OH and X is F, Cl, Br, I, CF_3, OCF_3, SCF_3, SCH_3 or Alk.

12. A compound according to any of the preceding claims, wherein R5 is selected from hydrogen, halogen atoms, alkoxy groups (AlkO-), alkylamino groups (AlkNH-), dialkylamino groups (Alk_2N-), carboxamido groups (-$CONH_2$, -CONHAlk, -$CONAlk_2$), acylamido groups (-NHCO-Alk), nitrile, lower alkyl groups, -CF_3, -OCF_3, -SCF_3, -SCH_3.

13. A compound according to any of the preceding claims in amorphous or crystalline form.

14. A compound according to any of the preceding claims in racemic or enantiomeric form.

15. A compound according to any of the preceding claims in the form of a physiologically acceptable salt, complex, solvate or prodrug thereof.

16. A compound according to any of the preceding claims for use in medicine.

17. A compound according to any of the preceding claims, which is an agent for preventing or treating diseases caused by or involving a melanin-concentrating hormone.

18. A compound according to any of the preceding claims, which is modulating the activity of a MCH receptor.

19. A compound according to any of the preceding claims, which has antagonistic activity against a MCH receptor.

20. A compound according to any claim 1-18, which has agonistic, inverse agonistic or allosteric activity against a MCH receptor.

21. A compound according to any of the preceding claims, wherein the MCH receptor has at least about 80% such as, e.g. at least about 85% or at least about 90% homology to the amino acid sequence CTLITAMDAN or CTIITSLDTC

22. A compound according to any of the preceding claims, wherein the MCH receptor comprises the amino acid sequence CTLITAMDAN or CTIITSLDTC.

23. A compound according to any of the preceding claims, wherein the MCH receptor is a MCH1 or MCH2 receptor.

24. A compound according to any of the preceding claims, wherein the MCH receptor is a MCH1 receptor.

25. A compound according to any of the preceding claims, wherein the MCH receptor is a mammalian such as human receptor.

26. A compound according to any of the preceding claims, which is an agent for preventing or treating feeding disorders.

27. A compound according to any of claims 1-19 or 21-26, which is an agent for reducing body mass.

28. A compound according to any of claims 1-19 or 21-27, which is an agent for preventing or treating Syndrome X (metabolic syndrome), or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension.

29. A compound according to any of claims 1-19 or 21-28, which is an agent for preventing or treating Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM).

30. A compound according to any of claims 1-19 or 21-29, which is an agent for preventing or treating bulimia, obesity and/or bulimina nervosa.

31. A compound according to any of claims 1-25, which is an antidepressant and/or anti-anxiety agent.

32. A cosmetic method for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto, the method comprising administering to an animal such as, e.g. a human in need thereof, an effective amount of a compound according to any of claims 1-19 or 21-30.

33. A method for the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-31.

34. A method for the treatment and/or prophylaxis of diseases caused by feeding disorders, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-30.

35. A method for modifying the feeding behaviour of a mammal, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-30.

36. A method for the reduction of body mass, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-19 or 21-30.

37. A method for the treatment and/or prophylaxis of Syndrome X (metabolic syndrome) or any combination of obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-19 or 21-30.

38. A method for the treatment and/or prophylaxis of Type II diabetes or Non Insulin Dependent Diabetes Mellitus (NIDDM), the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-19 or 21-30.

39. A method for the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-19 or 21-30.

40. A method for the treatment and/or prophylaxis of depression and/or anxiety, the method comprising administering to a mammal in need thereof an efficient amount of a compound according to any of claims 1-20 or 31.

41. A pharmaceutical composition comprising a compound according to any of the claims 1-31 or a physiologically acceptable salt thereof together with one or more physiologically acceptable excipients.

42. A pharmaceutical composition according to claim 41, wherein the compound is present in the form of a physiologically acceptable salt such as a salt formed between the compound and an inorganic acid such as e.g., a hydrochloride, a hydrobromide, a hydroiodide, a nitrate, a nitrite, a H_3PO_3 salt, a H_3PO_4 salt, a H_2SO_3 salt, a sulfate, a H_2SO_5 salt, or a salt formed between the compound and an organic acid such as organic acids like e.g. H_2CO_3, acetic acid, C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_5(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, lactic acid, citric acid, tartaric acid, ascorbic acid, benzoic acid, salicylic acid and phthalic acid.

43. A pharmaceutical composition according to claim 41 or 42 for enteral and/or parenteral use.

44. A pharmaceutical composition according to claim 41 or 42 for oral, buccal, rectal, nasal, topical, vaginal or ocular use.

45. A pharmaceutical composition according to any of the claims 41-44 in the form of a solid, semi-solid or fluid composition.

46. A pharmaceutical composition according to claim 45 in solid form, wherein the composition is in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, or particulate material.

47. A pharmaceutical composition according to claim 45 in semi-solid form, wherein the composition is in the form of a chewing gum, an ointment, a cream, a liniment, a paste, a gel or a hydrogel.

48. A pharmaceutical composition according to claim 45 in fluid form, wherein the composition is in the form of a solution, an emulsion, a suspension, a dispersion, a liposomal composition, a spray, a mixture, or a syrup.

49. A pharmaceutical composition according to any of claims 42-48 comprising a therapeutically effective amount of a compound according to claims.

50. A pharmaceutical composition according to claim 49, wherein the amount is from about 0.001 mg to about 1 g such as, e.g. from about 0.005 to about 750 mg, from about 0.01 to about 500 mg, from about 0.05 to about 500 mg, from about 0.1 to about 250 mg, from about 0.1 to about 100 mg or from about 0.5 to about 50 mg.

51. Use of a compound according to any of the claims 1-19 or 21-30 or a pharmaceutically acceptable salt thereof for the manufacture of a cosmetic composition for reducing overweight and/or for treating of and/or preventing overweight, bulimia, bulimia nervosa, obesity and/or complications thereto.

52. Use of a compound according to any of the claims 1-31 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for i) the treatment and/or prophylaxis of diseases caused by a melanin-concentrating hormone, ii) the treatment and/or prophylaxis of diseases caused by feeding disorders, iii) modifying the feeding behaviour of a mammal, iv) the reduction of body mass, v) the treatment and/or prophylaxis of bulimia, bulimia nervosa and/or obesity, or vi) the treatment and/or prophylaxis of depression and/or anxiety.